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ADVENTURES AMONG VIRUSES

II. Epidemic Influenza*

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DURING the past sixteen years influenza has been, I imagine, the virus that has received most study and attention in the laboratory, though poliomyelitis must run it very close. It has been studied by workers trained in very different disciplines and approaching it from many angles. Perhaps most novel and exciting is the work based on Hirst's[1] discovery of the power of the virus to agglutinate red cells of fowls. Directly deriving from this finding is the demonstration that influenza virus, or a part of it, has an enzyme-like action upon a carbohydrate-containing protein; this protein is present in serum and other body fluids and occurs on the surface of red cells and apparently also of the susceptible cells in which the virus can multiply. It is tempting to believe that the enzyme action plays a part in effecting entry of the virus into the host cell. As a result of these studies we can begin to picture as never before something of the biochemical basis of the attack of an animal-pathogenic virus on a cell, and we can demonstrate activity of a virus in a milieu other than the interior of the cell. Where all this will lead it would be rash to prophesy, but the prospects of swift advance are great.

My approach today is as different as can be. Instead of looking at the attacked cell and the individual virus particle adsorbed upon it, I wish to consider the ultimate results of that attack, not merely as it affects the patient's respiratory tract but as the resulting disturbance spreads to his family, his township and possibly over a large part of the world. The epidemiology of influenza has caused the spilling of much ink, for an influenza epidemic can be one of a drama on a large scale. Much of what has been written came at a time when we did not know that there was a virus of influenza, still less that there were two antigenically unrelated viruses, A and B. That knowledge might have saved much trouble to the earlier mathematician-epidemiologists trying to work out cycles of periodicity. There is much to puzzle us in the way in which influenza epidemics arise. Seven years ago R. E. Shope[2] gave a very stimulating Messenger Lecture on "Recent knowledge concerning influenza" and considered this puzzle; and in the same year I gave an address entitled "Thoughts on the Origin of Influenza Epidemics."[3] Our discourses ran on rather similar lines, and I shall refer to them again. Since then much water has flowed under London Bridge, and it is not, I think, too soon to have another look at this problem, though we are still far from seeing to its heart.

May I first remind you of certain characteristics of the influenza virus. It is not one of the viruses that invade the blood stream, and we may note in passing that many viruses that do cause such a generalized infection — such as those of measles and yellow fever — tend to give rise to a life-long immunity. Influenza doubtless enters our bodies through the air we breathe and attacks the superficial mucous membranes of our respiratory system, probably all the way down from the nose, by way of the pharynx and trachea to the finer bronchioles. Damage to these invaded cells accounts for many of the symptoms of the disease, and absorption of products of damaged cells for others. Lately, the Henles[4] and others have shown that influenza virus, apart from any ability to multiply, has a toxin-like action demonstrable in mice or rabbits. On the whole this toxic effect is associated only with intact living virus, but it is just possible by minimal treatment with ultraviolet rays to destroy infectivity while retaining some toxicity. Probably because it can attack us through the exposed surface of our mucous membranes and does not have to run the gauntlet of the antibodies and leukocytes in our blood, influenza finds us unable wholly to resist it, only a year or two after we have endured a visit from it.

Its ability to come back at us, after we have once repelled it, is probably due in part also to its plasticity. There are two influenza viruses, A and B,

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unrelated antigenically. Stories of two attacks of influenza within a short time may be explained by infection first with A and then with B; such occurrences have on several occasions been proved by laboratory tests. (Alleged repeated influenza attacks at frequent intervals are almost always not influenza at all.) But within the group of influenza A are serologic variants of such magnitude that vaccination with another strain of the A virus is unavailing against a new strain. It seems likely that the virus can vary antigenically, enough to upset the calculations of the epidemiologist, who would like to perceive regular cycles on his charts. With greater knowledge we may hope to interpret epidemiologic charts on the basis of rate of fall of immunity of a people, if we can combine this knowledge, with some insight into the maneuvers of the virus in the field of antigenic variation.

In 1899 Pfeiffer described the small gram-negative bacillus now called *Haemophilus influenzae*; this is known as the influenza bacillus and was for years thought to be the cause of influenza. During the terrible 1918–1919 pandemic it was in many areas present in enormous numbers in the lungs in fatal cases. There is no doubt now, however, that in other areas its activity was less noticeable and that other organisms replaced it as the most important secondary invaders. I say "secondary"; secondary to what? Attempts during that pandemic to demonstrate a causative virus, even using human volunteers, were mostly negative or unconvincing. Nevertheless, most people believe today that that pandemic was due to a virus, probably a variant or mutant of A, and perhaps one with a particular aptitude for acting in concert with bacteria, especially *H. influenzae*. Shope[5] has shown that the typical picture of swine influenza in the Middle West is due to combined attack by the swine-influenza virus and *H. influenzae* both closely related to their human counterparts. Human-influenza virus can also infect swine[6] but apparently co-operates less effectively with *H. influenzae suis*. Swine influenza occurs also in Europe, but here *H. influenzae* seems to be often of no special importance as an infection co-operating with the virus.

During an epidemic of influenza in man, a varying number of subclinical infections occur; these are usually recognized by the development of antibodies during the epidemic in persons giving no history of symptoms. After the epidemic, the virus seems to disappear. In Britain we have some influenza A roughly every other year, and virus A is to be found only for three months out of every twenty-four. From cases of clinical influenza occurring between epidemics we, at Hampstead, have always failed to obtain virus or serologic evidence of virus activity. Elsewhere, virus has occasionally been picked up from such sporadic cases, but I myself doubt whether the carry-over of virus from one epidemic to another can occur through the medium of such cases.

You will be familiar with Shope's[7] experiments, which show how swine influenza can be carried over from one year to another. The virus, which is really a strain of influenza A, may be carried from the lung of infected pigs in the ova of lung worms inhabiting the pig's lungs at the time. The embryonated ova passed in the pig's feces are taken up by earthworms; the lung worms go through stages of their developmental cycle in the earthworms and get back to the pig when it next has an earthworm meal. Virus is not directly demonstrable in the worms, but exists in a masked form. Influenza is not caused at once when the virus gets back to the pig; some jolt is necessary to activate it. The evidence for all this seems good, though so far as I know no one in any other laboratory in Europe or America has tried to repeat it. It seems unlikely to have universal applicability, for pigs in Britain have swine influenza though they may live their lives on concrete and may become bacon without ever seeing an earthworm. Another mechanism of carry-over is possible here; the virus of swine influenza has been recovered from chronic lung lesions in British pigs,[8] months after occurrence of the disease, and the same statement is true on the continent of Europe. One thing worries me about Shope's experiment: such a complex association between creatures of four species has the hallmark of an ecologic happy family, the result of eons of evolution. Yet neither the pig nor the earthworm concerned is native to the United States, and swine influenza is asserted never to have been known in the Middle West before 1918. It would be odd if swine influenza, which is not known to survive so long anywhere else (except in the virologist's dry-ice container), should just happen to find the interior of a lung worm an ideal resting place. I feel that either there is something wrong with the facts as presented or we ought to be looking rather more earnestly for some similar mechanism to explain the survival of human influenza viruses.

So much for our general background. We see two viruses, A and B, each capable of variation in antigenic and doubtless other characters, both attacking the surface of the respiratory tract and perhaps for that reason not generating life-long immunity, liable at times but not at other times to team up with a hemophilus and able to cause subclinical as well as clinical infections but — except for Shope's swine influenza — lacking visible means of support between one epidemic and the next.

Now for the epidemiologic background,[9] let us go back a hundred years or so. There was a good deal of influenza in Britain in the years preceding 1847-1848, when there was a serious epidemic. Then for many years the disease remained rather quiet — apart from two minor episodes — both in Europe and in North America. In the

decade prior to 1889 it was hardly recognized. There were, however, epidemics in Russia in 1886 and 1887. (Note these, for it was in Bokhara in central Asia that pandemic influenza reappeared in May and June, 1889.) From here it spread to other parts of Russia, to Europe generally and all over the world. In many parts it occurred as a series of waves; indeed one hardly knows how long they went on, for the incidence of influenza has never since fallen back to the low pre-1889 level. Professor Greenwood thinks that this phenomenon is genuine and not a reflection of changing fashions in nomenclature, that it is true that "the position lost in 1890 has never been regained." I confess that the change in incidence worries me a lot. We can recognize the presence of influenza A and B viruses in Britain at best every other year. Why then is the mortality attributed to influenza higher *every* year than before 1890? Figures from Australia, I may add, are much the same as those from Britain.

The 1889–1890 pandemic was extensive and severe, but it *was* ordinary influenza. The 1918–1919 pandemic was very different in its heavy and lethal attack on young adults. Ordinarily, those killed are the very young and the very old. Prior to 1918, the disease had not declined as it had before 1889; indeed, Frost, in the United States, had noticed some signs of buildup from 1914 on. The origins of the pandemic in 1918 are rather obscure. There had been an epidemic early in 1918 in North America and the disease appeared in France among American troops at Brest and Bordeaux in April. It reached Britain in June, possibly through the agency of troops returning on leave. If we take as the hallmark of 1918 influenza the killing power for young adults, we should look for its origin to a country where there was a *gradual* development of a high mortality in young adults, as, presumably, the new strain got under way and replaced the ordinary influenza. In Britain in June the epidemic showed a *sudden* change in age incidence of mortality: Burnet and Clark[9] argue that the vicious new strain cannot therefore have arisen in Britain. They failed to obtain adequate data from other countries but seem by implication to suspect an origin in France or perhaps among the American soldiers traveling across the Atlantic. They speak of the primary European-American center of origin. Boston was the first place in America to experience influenza in its severe form, and, of course, Boston was a major port of embarkation for Europe. There are suggestions that a change to the virulent form may have occurred not only at this European–American center but also separately and independently in West Africa, in India and in central China.

We do not know and may never know what was the causative agent of the 1918 epidemic, but I think most workers suspect that it was a mutant of virus A — or possibly B. The emergence of a new mutant is largely a matter of chance, the chances being greater the more virus there is about and the more it is multiplying. If an ordinary influenza epidemic hits a community with rather low resistance and if there are unusual opportunities for its rapid spread, as by dense aggregations in troopships and camps, the chances are great that a new mutant may arise. There were successive waves of influenza in 1918–1919, and suffering from the disease in one wave did not necessarily protect one from attack in the next wave; these facts suggest that the mutant appearing in the summer of 1918 was an unstable one from which new mutants readily derived. It is thus not very improbable that a similar, second-stage mutant of especial virulence arose independently in several countries to which the first mutant strain had spread. The new strains presumably differed in antigenic makeup and in greater tendency to attack the lungs. The first mutant had already shown some viciousness for young adults, and this propensity developed further.

I wish to consider the 1918–1919 epidemic only in its relation to the influenza that preceded and followed it. In my first lecture I discussed the properties of viruses and how virulence on the one hand and persistence or power to survive through hard times on the other were qualities that rarely went together. We must, I think, believe and be grateful that the 1918 virus, though its virulence allowed it to kill 15,000,000 people, lacked the small quality of persistence possessed by, say, the humble herpes virus. It cannot have died out at once after 1919, for there was a gradual return to normal age incidence of mortality over several years. This was reached in the United States at least by 1923; in Britain it apparently took rather longer. A gradual replacement of the pandemic strain by ordinary influenza viruses seems a rational explanation. A gradual change in the properties of the virus is also a possibility. Consider what happened in a country that escaped the pandemic but was attacked soon after. New Caledonia escaped in 1918, but influenza was introduced there in 1921. The incidence was very high, but there is no suggestion that mortality was high in young adults. Those who, having been away from the island, had been through the 1918 pandemic elsewhere, had apparently lower susceptibility to this 1921 outbreak than others on the island.

Influenza has behaved differently in England since 1920, on the basis of the weekly deaths recorded as due to influenza for the 126 great towns of England and Wales. The general practitioner's diagnosis of influenza would not, one would think, be very reliable, for no one can diagnose a case with confidence. Nevertheless, his diagnosis of influenza as a cause of death bears a most remarkable relation to the activity of influenza, usually virus A. The deaths seem largely to be among old or weak people upon whom the virus administers a *coup de*

grâce. Possibly, the doctor tends to put influenza on his death certificates when there is a lot of upper respiratory infection in his practice. Anyway, these notifications are of great help to us. Before the war, influenza tended to attack us every other year, with special emphasis on every fourth year. Since 1939 the spacing between epidemics has been rather wider, and the peaks rather lower. Before, however, we start congratulating ourselves let us remember that influenza seemed to be fading out before 1889.

As to what starts an epidemic, there are two main theories. According to one view influenza is always with us. At times of epidemic, an endemic virus lights up, perhaps because the immunity of the population has fallen to a low enough level or because of some climatic or other unknown factor. The reported spread of the disease from country to country is thus only apparent; there is really a successive activation in each country of its home-bred virus. Certainly there is at times a wildfire spread of influenza, too rapid to be conceived of as due to ordinary spread by human contacts. In Shope's[9] Messenger Lecture referred to above, he describes most graphically the beginnings of a swine-influenza outbreak in the Middle West. On one day a drove of 100 animals seems perfectly well; next morning the whole lot are off their food and depressed, and by the next day the "illness is full-blown," and a few may be dead. This is not an isolated occurrence, for "within five miles . . . there are two dozen other swine herds concurrently undergoing influenza" — with, mark you, no direct contact between them. The owner of one herd puts it all down to the animals' sleeping in a draught because a door was left open, or to some similar cause. One can, however, hardly believe in an epidemic of leaving doors open, afflicting two dozen farmers simultaneously. Shope suggests that the virus has been seeded into the herd by the agency of the earthworms carrying the virus and that some jolt has activated the infection. He goes on to inquire whether a similar state of affairs may not occur in human influenza and quotes in support some data from a thesis by Robert Johnson,[10] of Philadelphia, published in 1806. This far-seeing doctor noted that influenza seemed to travel more rapidly than means of human transport and that during an epidemic "even persons at sea, though at an immense distance from land, were affected in the same manner" as those ashore. Johnson could not bring himself to believe that influenza was due to a specific contagion. If so, "it must always exist. The small pox, the venereal disease, etc., never intermit; but the influenza has become extinct and again broke forth upon the world after a period of . . . years." Shope, in discussing these ideas, suggests, as his studies of swine influenza naturally incline him to do, "a pre-epidemic seeding of the causative agent of the human disease."

The opposite view concerning influenza epidemics is that some other country is always to blame. In 1889-1890 it was called "Russian 'flu" with some justification; in 1918 it was "Spanish 'flu" for no particular reason at all. I myself felt rather chilly toward the idea of country-to-country spread, until in 1945–1946 there was an almost world-wide pandemic of influenza B.[11] It is hard to believe in conditions changing within a single year from Australia to the Caribbean and across to Europe, all favoring B, the poor relation of the influenza A virus. Apparently, noteworthy B outbreaks began in mid-Pacific, in Guam and Hawaii in June, 1945, though there had been some in the United States in the previous March. From the Pacific the virus went east to the Caribbean, the northern parts of South America and Texas. A rather slow spread occurred in the United States. The B virus also went south to Australia (November, 1945) and farther east to Europe, reaching Holland and Belgium in December, 1945, and England in January, 1946. Serologic study showed that Australian and British strains were closely related and rather different from the standard B strain. There were also epidemiologic similarities between the B strain in Australia and that in Britain; in both countries school children were particularly affected. I have gone a little beyond my facts in thus describing the epidemic, for we have not serologic proof from every country in its track that it was B that was active; not every country was equipped to make the necessary tests.

Need for accurate information in such circumstances is great. Only thus can we learn the facts upon which we can judge if country to country spread of influenza is a real phenomenon or an illusion. Largely for such reasons, the World Health Organization set up, at the National Institute for Medical Research at Hampstead, a world influenza center. In this laboratory, which is quite small and unpretentious, we hope to gather strains of influenza from outbreaks all over the world, as well as information about the activity of the disease. Recently, I am glad to say, Dr. Magill, of Long Island Medical College, has agreed to be responsible for a corresponding laboratory over here, a continental strain-study center, dealing with both North and South America. This has been arranged in consultation with the United States Public Health Service and Army Influenza Commission. And now the antigenic variability of influenza, which is in general such a nuisance, becomes a positive asset, for it is possible to track a particular strain across a continent. We may have been lucky in 1948–1949 in having a nice, unsmirched bloodhound trail across Europe. The slide shows the progression of influenza last winter from an origin in northern Sardinia in late September and October, 1948. It appeared a little later in Sicily and Calabria, though whether arising independently or

coming from Sardinia I should hesitate to say. Thence was a regular spread up Italy, into Austria, Switzerland, all over France, into northern Spain and western Germany and across Belgium into Holland. All these countries were reached by December, 1948, or January, 1949, and in most of them the incidence was very high. First cases were recognized in Britain about the New Year in people newly arrived from France, but the disease took some weeks to get under way and was not nearly so widespread as on the Continent, although it is not regarded as one of our major outbreaks. The virus also reached Denmark, apparently by sea, and Iceland. Besides the A epidemic a small B outbreak was recognized in Italy, England, Denmark, Sweden and across the iron curtain in Czechoslovakia, Hungary and Jugoslavia, but apparently that curtain stopped the large A outbreak. Freedom of communication across frontiers and ideologic climate clearly cannot explain all, for Sweden had only a sporadic A epidemic. One can, however, perhaps explain this, and also the lower incidence in Britain and the failure to spread to America, by the prevalence in those countries of a related virus only two years before, in 1947. Jugoslavia had quite a large outbreak of respiratory infection this year, but, judging from the results of tests on serums from there and on clinical reports, we cannot conclude that this was influenza at all. Turkey had an A outbreak, whose relations to that in western Europe are doubtful.

I have talked confidently of a real spread. I do so because we received viruses from Italy, Switzerland, France, Holland, Britain and Iceland, and these were antigenically identical. My colleague, Dr. C. M. Chu, found that they were of the aberrant type of A known as A-prime, but, though of this general type, they were by refined serologic methods demonstrably distinct from the A-prime strains recovered from Australia, America and Europe in 1946 and 1947. The homogeneity of the 1949 viruses contrasts with results obtained in 1937 when several serologic types were obtained in one epidemic, mostly from near London.[12] In those days we adapted all our strains to mice and carried out neutralization tests in mice with the aid of immune ferret serums. Nowadays we use fluids from infected eggs and study these with the Hirst and complement-fixation tests. Was the antigenic homogeneity due to use of a different technic? Apparently not, for I tested four 1949 strains by the 1937 methods and found them still identical. They did, however, do what Hirst[13] has described in showing some antigenic divergence after many passages through mice.

The origin of this epidemic has been studied in Sardinia by Magrassi,[14] who took good advantage of his favorable position on an island. From mid-September, 1948, to early October a simultaneous multicentric origin was noted in ten inhabited centers in northern Sardinia. The peak of morbidity was reached after thirty or forty days; incidence was up to 60 per cent. When the wave was declining at the end of October a second group of seventeen centers became affected. Magrassi thinks that this second burst of activity may have also been autochthonous. "There seems," he says, "never before to have been given such a clear and precise demonstration of a multicentric origin of influenza in a relatively restricted stretch of territory and in tolerably uniform geographical conditions and environment, such as was encountered in Sardinia." He adds, concerning the second outbreak "we were able to verify, for example, the appearance of a typical form of influenza in shepherds who were living for a long time alone, in solitary open country many kilometres from any inhabited centre; this occurred absolutely contemporaneously with the appearance of influenza in the nearest inhabited centres."

An interesting aspect of this autumn outbreak is that figures from Italy show that influenza was prevalent in the late spring and early summer of 1948 in Sardinia, Sicily and Calabria — just those provinces in which the outbreak began first in the autumn. It looks as though the epidemic went underground in the unfavorable summer months, to reappear as conditions became more propitious with cooler weather. It is true that the late spring outbreak was allegedly caused by the B strain. Even so, the course of events recalls happenings in Canada, the United States and Britain in 1943. In those countries there were sporadic early summer outbreaks of A influenza (in Britain after an earlier B outbreak); these ceased, but A reappeared in September to cause one of the largest outbreaks of the past decade.

Other incidents combine to impel our thoughts in a certain direction. Outbreaks of common colds frequently occur in the local inhabitants soon after a ship touches an isolated port. But in November, 1935, a serious outbreak of influenza started in Angmagsalik in Greenland more than two months after the visit of a ship from abroad. I was recently reading for relaxation a travel book, *Exploring with Byrd*, and found an account of "a really severe influenza epidemic, about 40% of the men suffering" at Byrd's base camp in the Antarctic. This was on January 6, 1929; they had left New York in the early autumn and New Zealand on December 12, 1928. New Zealand had no influenza that year, but New York *had* and, so far as I can make out, had it at about the same time as did the detached piece of America in the Antarctic called Little America. Had something been slowly building up in Byrd's party, just as in the America they had left?

Magrassi[14] writes, "migration of an individual carrier of the infection into new groups of population is insufficient to give rise to influenza." Per-

haps that is why after some cases reached Britain in early January it took such a long time for influenza to flare up. Everything suggests to me that an influenza epidemic is like a burst of flame set alight when a spark traveling along a slow fuse has reached the end of its journey. Hirst and others have found serologic evidence of occurrence of isolated subclinical infections with influenza some weeks ahead of the epidemic, but the activity of the slow fuse is usually hidden from our knowledge. Why do colds light up when the cold weather begins in the autumn, whereas influenza only exceptionally starts then, occurring more commonly in late December and early January? May it not start earlier than we think, but in the unseen fuse stage of its existence?

In my 1942 lecture referred to earlier, I suggested that influenza might exist in several grades of virulence; there would be a Grade I or basic virus adapted to perpetuating itself as a latent infection and lacking the A antigen by aid of which we could recognize its presence. As it built itself up through Grades II, III, IV and V it acquired in stages A antigen and ability to infect ferrets and mice and to spread better and better in man. Finally Grades VI and VII were the first-stage and second-stage mutants of pandemic virus that we discussed earlier. Perhaps this conception should be dismissed as the sort of naïve idea to be expected from a young man of under fifty. Nevertheless, I still feel that there may be something in it. The acquisition of successive grades of virulence is an idea akin to that of the slow fuse. It seems that when a few sparks — infective cases — reach a new area, they will exceptionally find dry tinder ready for them, but will more often merely start off the smouldering of a fuse of greater or lesser length.

The conception that virus particles vary quantitatively in virulence and power to spread affords a basis on which one can happily speculate for hours about the mechanism of epidemics. Topley's studies on the epidemiology of mouse typhoid were, however, all against such a view. Another factor must, in any case, be considered also. In general, one is happy to have successfully isolated influenza virus from a throat washing by egg inoculation; one does not readily succeed with diluted washings. But several workers, including Hirst,[13] have encountered occasional subjects who have yielded throat washings positive for virus at 1:1,000,000 dilution. Just as nasal carriers of hemolytic streptococci seem important in the epidemiology of streptococcal infections, so the occurrence of a few super-shedders of influenza virus may be of vast importance in our problem. We have often been puzzled, during lesser outbreaks, to explain how influenza can pick, let us say, on one company of recruits and lay it low, whereas others in a similar environment are almost spared. The presence of one super-shedder in a company might explain a lot.

On the whole I feel that there may be no incompatibility between the two theories I have mentioned concerning the beginning of epidemics. There may be a county-to-county spread of virus but not necessarily of an immediate epidemic. The immigrant virus may spread at first unnoticed and burst out later on, causing an outbreak of apparently multicentric origin.

We have now collected a few ideas on the buildup and spread of epidemics, but are no nearer understanding where the virus goes between outbreaks. If our fuse is, as seems likely, so constructed that it burns faster and faster as it goes on, tracing it backward would bring us to a fuse burning very slowly indeed. Indeed, I suspect that the smouldering of influenza between outbreaks is so slow and inefficient that it often goes out. It seems to have gone almost out in the 1880's. In small isolated communities such as St. Helena it seems to die out until reintroduced. Just by luck, now in Bokhara, now in Sardinia, some fortuitous set of circumstances lights a fuse that later starts a fire. Recent antigenic studies of virus A themselves suggest that its continued existence always hangs on a slender thread. Almost all A outbreaks since 1947 have been associated with the apparently novel A-prime strains. Where are the viruses allied to the older W. S. and PR8 strains, which caused our troubles between 1933 and 1946? Have their fuses all fizzled out?

Some years ago there was talk of whether swine influenza in the Middle West was passed to swine during the pandemic from man. It seems equally relevant to consider whether virus may not pass from pig to man, the pig being a reservoir of human influenza. The swine virus has apparently worked out a fool-proof mechanism for carrying on in worms between epidemics. Perhaps just now and again a mutant of swine influenza becomes adapted to a human host. I suggested recently that we now had available a means of obtaining information on this point. Shope's swine-influenza strains from Iowa stand antigenically apart from other A viruses. Swine viruses from Cambridge (and I mean Cambridge, England, not Cambridge, Massachusetts) and from Northern Ireland are just as closely related to the PR8 strain of A as to Shope's virus. If currently isolated swine viruses proved to be of the same nature as those now prevalent in man — that is, of the A-prime variety — we should have to look into this question of possible pig-to-man infection more carefully. And now comes the news that a swine virus isolated in Korea in 1939, the Oti strain, bears some relation to the A-prime group. I am glad to say that at the International Veterinary Congress, held in London in August, decisions were taken to arrange serologic comparisons of swine-influenza viruses from many countries, much as we are doing with human viruses.

Possible persistence of influenza in other species must be borne in mind also. Dr. S. G. Anderson, in unpublished experiments in Burnet's laboratory, found suggestive evidence that sheep might be susceptible. With this in mind I managed to obtain by the kindness of Professor Magrassi serums from the sheep belonging to some of his solitary shepherds, but, alas, no specific antibodies were demonstrable.

Finally, let us ask what the prospects of a return of a pandemic like that of 1918–1919 are. Frankly, we know so little that we can only guess. Influenza seems to be a megalomaniac virus that likes to operate on a world-wide scale. It has to be labile to adapt itself to a changing civilization. Dare we hope that civilization is changing too fast for it? If pandemics occur in a country when immunity to the virus has reached a low ebb, may they not be averted if air transport and increased travel generally cause a mixing-up of all peoples and their viruses, so that our immunity never falls too low? Naturally, one foresees a possible danger: if political troubles should cause a further division of the world into two separate camps, different strains of influenza might become dominant in each half, the other half of the world having no immunity to it; the virus, which has no political preferences, would then seize its chance.

In a world where, by and large, infectious disease is waning as a factor holding up human progress, influenza stands out as a still-present menace. It is a disease of such fascination that one would be almost, but not quite, sorry to see it go.

References

1. Hirst, G. K. Quantitative determination of influenza virus and antibodies by means of red cell agglutination. *J. Exper. Med.* **75**:49-64, 1942.
2. Shope, R. E. Swine influenza. In *Virus Diseases, by Members of the Rockefeller Institute for Medical Research.* 170 pp. Ithaca, New York: Cornell University Press, 1943.
3. Andrewes, C. H. Thoughts on origin of influenza virus. *Proc. Roy. Soc. Med.* **36**:1-10, 1942.
4. Henle, W., and Henle, G. Studies on toxicity of influenza viruses. *J. Bact.* **51**:632, 1946.
5. Shope, R. E. Swine influenza: filtration experiments and etiology. *J. Exper. Med.* **54**:373-385, 1931.
6. *Idem.* Serological evidence for occurrence of infection with human influenza virus in swine. *J. Exper. Med.* **67**:739-748, 1938.
7. *Idem.* Swine lungworm as reservoir and intermediate host for swine influenza virus: transmission of swine influenza virus by swine lungworm. *J. Exper. Med.* **74**:49-68, 1941.
8. Blakemore, F., Gledhill, A. W., Glover, R. E., and Taylor, E. L. Discussion on swine influenza in British Isles. *Proc. Roy. Soc. Med.* **34**:611-618, 1941.
9. Burnet, F. M., and Clark, E. *Influenza: A survey of the last fifty years in the light of modern work on the virus of epidemic influenza.* 118 pp. (Hall Institute Monograph No. 4.) Melbourne: Macmillan, 1942.
10. Johnson, R. *On the Influenza.* 36 pp. Philadelphia: University of Pennsylvania, 1806.
11. News and Comment. Prevalence of influenza B. *Bull. U. S. Army M. Dept.* **4**:369, 1945.
12. Stuart-Harris, C. H., Andrewes, C. H., and Smith, W. *A Study of Epidemic Influenza: With special reference to the 1936-7 epidemic.* 151 pp. Medical Research Council Special Report Series, No. 228. London: His Majesty's Stationery Office, 1938.
13. Hirst, G. K. Comparisons of influenza virus strains from three epidemics. *J. Exper. Med.* **86**:367-381, 1947.
14. Magrassi, F. Studi sull'epidemia influenzal dell'autunno 1948: insorgenza, carattes: lazzione clinica ed eziologica dell'epidemia in Sardegna. *Minerva med.* **40**:565-569, 1949.

THROMBOEMBOLISM*

A Comparison of the Effect of Early Postoperative Ambulation and Dicumarol on Its Incidence

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THE brilliant contributions to the therapy of thromboembolism with venous interruption by Homans, Allen and their co-workers in Boston, with heparin by Jorpes and Bauer in Sweden, and with Dicumarol by Allen and Barker at the Mayo Clinic and Evans and Dee of the Lahey Clinic pose a practical problem in the selection and application of these methods that the community surgeon must resolve for himself. Prior to these definitive measures many so-called mechanical methods were used in the hope of reducing the incidence of this complication of surgery.

The present report outlines personal observations on the application of preventive therapy extending over several years. They are presented as possibly having lessons of value for the community surgeon. The several methods were applied to successive blocks of patients having at least 500 in each block. During the year 1944 all patients (674) were kept in bed for the traditional ten-day postoperative period; there were 18 cases of thrombotic complications, a rate of 2.7 per cent, with 1 death from embolism. In 1945 the patients (640) were permitted ambulation to the extent of 85 per cent of the group on the first to the third day; there were 15 thrombotic complications, a rate of 2.3 per cent, with 2 deaths from embolism. In 1946 the patients (504) were allowed out of bed on the third to the seventh day, with 12 cases of thromboembolism, a rate of 2.3 per cent, and with no deaths from embolism. In 1948 the patients (525) either were permitted ambulation on the first to the third day or given Dicumarol prophylactically. An abrupt drop in the incidence of thrombotic complications occurred to the number of 8 cases, a rate of 1.5 per cent, with no deaths from embolism.

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Ten-Day Bed Rest

During the year 1944 the patients (674) were kept in bed for ten days after operation. The 18 cases of thrombotic manifestations (2.7 per cent)

showed the following regional distribution; 3 after gall-bladder surgery; 4 after pelvic surgery; 3 after appendectomies; and 3 after surface surgical procedures (hernias and breast removals). The remainder were scattered through several types of procedures. They were never encountered after thyroid, rectal or pilonidal-cyst surgery. No emboli were observed after varicose-vein surgery. This group is not otherwise included in the percentages because of the difficulty of differentiating the usual postoperative disability of the wrapped sore leg due to multiple ligations, stripping and injections from a bona-fide thrombophlebitis.

The occurrence of thrombotic complications in these bed-confined patients after operation brings to mind several of the many factors regarded as contributory to the lesion. This experience has occurred in the New England Atlantic Seaboard area, where statistically the lesion occurs more frequently than elsewhere in the country. This area also encounters severe winters, which Favre notes is associated with a higher incidence of the disease, particularly when influenza epidemics are prevalent. The existence of an intrinsic factor of preformed clots in the legs is well known. DeTakats has pointed out that 50 to 60 per cent of adults carry thrombi in the plantar veins or the calf veins of the muscles in the lower leg. Rössle indicates that 27 per cent of persons over twenty years of age harbor such thrombi in the leg muscles.

Ambulation on the First to the Third Day

An effort was made to control these factors during the year 1945, when ambulation was permitted for 85 per cent of the patients (640) on the first to the third postoperative day. Other factors were controlled. In consequence of Frykholm's postulate that pressure of the calves on the bed caused trauma to the leg veins, with subsequent thrombosis, no pressure was allowed on the calf muscles from the minute the patient was placed on the operating table until after the first week of ambulation had passed. Paralleling the demonstration by Potts and Smith that a 250 per cent increase in blood flow in the extremities of animals occurred with the legs elevated and exercised, the extremities of these patients were elevated for the first week. Active foot exercises were encouraged because this was so favorably evaluated by Allen, Adams and others. Following the interest of Walters in stimulating the circulation by administration of desiccated thyroid, these patients received small doses of epinephrine in oil unless such therapy was contraindicated.

All reports on the effectiveness of such methods are not favorable, however. Smith noted an increased incidence of thrombotic complications after several measures, including active foot exercises. In this series despite all these measures, 15 thrombotic complications occurred — a rate of 2.3 per cent. Nine of these occurred after surgery in the pelvis, and 2 after surface surgery; 4 were scattered through several other surgical procedures.

Ambulation on the Third to the Seventh Day

There is controversy concerning what day of rising actually constitutes early ambulation. Consequently, during 1946 504 patients were allowed out of bed on a slightly delayed schedule, — the third to the seventh day, — which made possible ambulation of 95 per cent of the group. Twelve cases of thromboembolism were encountered, a rate of 2.3 per cent, which reflects the same rate of incidence that previously prevailed. These occurred in 2 cases in the gall-bladder group, in 2 after pelvic surgery and in 6 after appendectomies (5 patients having peritonitis).

The literature is confusing regarding the efficacy of ambulation in preventing intravascular clotting. Zava reported not a single embolus in 15,000 surgical cases with early ambulation; Leithauser encountered only 4 deaths from embolism in 15,000 cases so handled. However, Blodgett and others reported no reduction of thrombotic complications with early rising. Fine reported 5 cases of thrombophlebitis in one year with early ambulation. Failure to modify the rate of occurrence in the present study sustains the criticism of Allen, Linton and Donaldson that "it was felt that early ambulation might lower the incidence of thrombosis and embolism. There is considerable evidence against it and little to support it."

Limitations of Early Ambulation

Because many writers have manifested such enthusiasm for the protective role of early ambulation against thrombotic complications, it was believed that a selective review of failures of the method in this series would be instructive. Of a total of 13 thrombotic complications encountered despite the use of early rising, 8 occurred after ambulation on the first postoperative day, 3 were encountered after ambulation on the second postoperative day, and 2 were encountered after ambulation on the third postoperative day. One of these patients died suddenly on the fifth postoperative day from a massive embolus (cor pulmonale was demonstrated by the electrocardiogram). An important point is that 60 per cent of these failures after early ambulation occurred in patients past fifty years of age.

Ambulation and Dicumarol Regime

In 1948 the first prophylactic use of Dicumarol was undertaken in combination with early ambulation (525 patients). Patients over whom no hesitancy was felt were out of bed on the first to the third day. This method selected the youngish, vigorous, nonobese, well conditioned surgical patients in whom, presumably, thrombosis would

be least likely to develop. The only cases of thrombosis encountered during the year occurred in this group (1.8 per cent). The second and smaller group of bed-confined patients, composed of older, more obese, more depleted and sicker patients for whom concern was entertained over early ambulation, were given Dicumarol prophylactically. They received 200 or 100 mg. as indicated to bring them into a range of 40 to 50 per cent prothrombin index (24 to 29 seconds). They were kept in range until after the third day of active ambulation. No thrombosis occurred in this group. This combined routine produced a sharp drop in occurrence of the lesion to 8 cases in 525 patients, a rate of only 1.5 per cent. These were distributed as follows: 2 after surgery of the gall bladder; 2 after vaginal operations; and 1 each after a stomach and a bowel operation.

A few studies on prophylactic use of Dicumarol postoperatively have been reported. Barnes reports 832 hysterectomies with prophylaxis showing an incidence of thromboembolism in only 9 cases, when 80 might have been expected without prophylaxis. There were no deaths from embolism. Bruzelius notes a reduction by two thirds in the incidence of thrombosis and embolism in 1448 patients given Dicumarol prophylactically after operation. Smith observed a reduction in the complication after prophylactic administration of Dicumarol in gynecologic surgery. Wise and his associates report a rate of vascular complications of only 0.18 per cent in 3304 patients treated prophylactically, as compared with 1.6 per cent in an untreated group. Allen, Linton and Donaldson report a 25 per cent reduction of thrombotic complications in a group treated prophylactically with Dicumarol as compared with an untreated control group.

Dicumarol-Protected Group

There were 62 out of the 525 patients (12 per cent) who were confined to bed and given Dicumarol prophylactically. On the basis of age, there were 30 (about 50 per cent) over fifty years of age; 44 of them (about 70 per cent) were over forty years of age, and the remaining 30 per cent were twenty to forty years of age.

With reference to the type of operation 29 were cholecystectomies, 12 were pelvic operations, 7 were resections, and 14 were miscellaneous procedures. These 48 cases in the three specified groups constitute an isolated group with a potentially high exposure rate to thrombotic complications. Protection by means of Dicumarol reduced the over-all incidence of thrombosis to 1.5 per cent. This constitutes an indirect nonspecific method for isolating patients most likely to have thrombotic complications after operation.

Distributive Factors

Two major factors have emerged from the study as of measurable significance in the occurrence of thrombotic complications in usual community surgery — the age of the patient and the type of operation. Allen and his co-workers previously found that only 5 to 7 per cent of thrombotic complications occurred under thirty years of age, 12 per cent between thirty and forty years of age, and 80 per cent over forty years of age. With reference to the type of operation Barker, in analyzing 172,888 operations, found that the lesion occurred twice as frequently after laparotomies as in all types of operations, and three times as frequently after pelvic operations as after all other types of surgery. He reported an incidence of 4 per cent after pelvic operations, with a death rate from fatal embolism of 0.7 per cent.

In the present study the cumulative evidence of several aspects of the problem establishes fifty years of age as the critical point in a general surgical community practice after which thromboembolism assumes significant proportions. Of the patients permitted early ambulation exhibiting postoperative thromboembolism, 60 per cent were over fifty years of age; in the group with definite embolization, 78 per cent of patients were over fifty years of age, and of 5 patients with fatal emboli encountered during this period 4, or 80 per cent, were over fifty years of age. A recalculation of figures indicates a projected incidence of thromboembolism in general surgery after fifty years of age at a rate of 4.1 per cent. A comparable figure after hysterectomies was considered a proper reason to use Dicumarol prophylactically at the Mayo Clinic. Might not the same criterion be considered applicable to the surgical patient over fifty years of age in community practice? Charting the age distribution for a typical year of community surgery indicates that active Dicumarol prophylaxis in patients over fifty would require its use in only a

Table 1. *Operation Factor of Distribution (1944, 1945, 1946, 1948).*

Area	No. of Cases	Thromboembolism	
		No. of cases	Per-centage
Upper abdomen:			
Gall bladder, ducts	262	7	2.7
Stomach and spleen	71	1	1.4
Lower abdomen:			
Pelvis	326	17	5.2
Bowel	78	3	3.8
Appendix and exploration	513	10	1.9*
Vagina:			
Major	115	3	2.6
Minor	255	4	1.7
Surface:			
Extremities	185	1	—
Torso	466	6	1.3
(Breast, hernia, thyroid gland)			
Rectal, pilonidal cyst	83	0	0
Totals	2354	52	
Average			2.2

*Including cases of peritonitis; the rate was only 0.98 per cent if patients with peritonitis are excluded.

third of the patients operated on during the year. Yet its protective role would be exerted on the two thirds of the patients most exposed to the threat of thromboembolism.

The factor of the type of operation in the incidence of thromboembolism in this group seems clearly delineated by the cumulative group incidence for the entire 2354 cases observed during the four-year period (Table 1). In the pelvic group of 326 cases representing 1 in every 7 operations the rate was 5.2 per cent; in the gall-bladder group of 262 cases representing 1 in every 9 operations the rate was 2.7 per cent; in the 78 bowel operations representing 1 in every 30 operations the rate was 3.8 per cent; in the 513 appendectomies representing 1 in every 4 operations the rate was only 1.9 per cent, inclusive of the peritonitis cases, and only 0.98 per cent when the cases of peritonitis are excluded — a negligible incidence.

Embolism and Infarction

Despite the potential severity of symptoms arising in the extremities from the late local sequelae of thrombosis — chronic venous insufficiency with edema, varices, ulcers and indurative cellulitis — attention has been centered mostly on the dramatic and hazardous occurrence of embolization with infarction. The rate of embolization in 1945 with very early ambulation was 1.2 per cent; in 1946 with delayed early ambulation it was 1.5 per cent; and in 1948 with the combined ambulation and Dicumarol regime the rate dropped to 0.76 per cent. As already stated 78 per cent of emboli occurred in patients over fifty years of age. Women were involved in 70 per cent of the cases, but this exactly parallels the 70 per cent preponderance of surgical procedures among women in a typical year of general surgery in a community.

The fatal emboli, 5 in number, occurred with 1 exception in patients over fifty years of age. This gives an over-all incidence of 1 in 563 cases. All patients died with a typical clinical episode of embolization; all had normal electrocardiograms preoperatively, except 1 with moderate myocardial changes. One embolism was proved at autopsy (permission for autopsy was not obtained in the other cases), and 1 by an electrocardiographic tracing typical of cor pulmonale. All occurred in women who, with 1 exception, were obese.

Discussion

This study presents a continuing experience from 1944 through 1948 in which, in successive blocks of 500 or more patients, various methods were used to control thromboembolism. In the year 1947 the problem was disregarded, and no personal bedside notes were maintained on which the rest of the study is based. Hence the 1947 period is not included in the study. No effective reduction in the rate of thromboembolism was accomplished until 1948, when Dicumarol was used prophylactically in patients confined to bed who usually were over fifty years of age.

The patients fifty years of age or over constitute a selected group in whom to study the efficacy of protection by Dicumarol. In addition to the 30 patients over fifty years so protected in 1948, more than 70 patients over fifty were so protected with a continuing study during 1949. Thus, more than 100 patients over fifty years of age were kept entirely free from thromboembolic complications. From my experience during the full period of this study, 4 cases might well have been experienced in this group. All other methods of management have been essentially the same, except that there has been a shift toward more use of cyclopropane and curare for anesthesia. However, a breakdown of the groups previously had shown no particular relation to the type of anesthesia used, thrombotic complications occurring with all types. The same preoperative and postoperative management of the patients prevailed. Ambulation has always meant active walking by the patient, beginning with two short periods a day after operation as indicated in the yearly groups, and rapidly increasing until the patient is walking around the hospital corridors by the fifth or sixth postoperative day. Sitting in a chair was not permitted, in line with current opinion in such studies.

The use of Dicumarol has been without untoward incidents since the range for protection was established between 40 to 50 per cent prothrombin index. The determinations in the laboratory are dependable and are available at all times, including week ends and holidays. Otherwise, hesitancy would be felt in administering successive doses of the drug because of the possibility of sensitivity. Sensitivity in the patients over fifty years of age was controlled by restriction of initial doses to 200 mg. from fifty to sixty years of age, 100 mg. from sixty to seventy years of age, and 50 mg. after seventy years of age. When sensitivity was ruled out, regular doses of 100 mg. were administered. A total average dose of 500 to 800 mg. was administered over all age groups until the patients were vigorously ambulatory by the fifth to sixth days. The patients were then permitted to come out of range spontaneously. Hykinone (72 mg.) was administered in one or more doses as needed in elderly patients whose prothrombin index dropped below 40 per cent, to patients who were not out of range at the time of discharge, and to patients in whom blood leaked from the operative field. No significant bleeding was encountered in the group with the routine administration of the drug begun on the second postoperative day. With a lower level established at 30 per cent prothrombin index during the initial period of the study, serious bleeding from the operative field requiring transfusion was encountered. For this reason the prophylactic level

of 40 to 50 per cent prothrombin index was arbitrarily established, and no significant bleeding has been encountered with blood levels in this range.

Summary

A continuing four-year study on control of postoperative thromboembolism showed failure to modify the rate of incidence of the lesion except with the adoption of Dicumarol prophylaxis.

The incidence of thrombosis was a fairly constant figure of about 2.5 per cent with ten days of bed rest (1944), with ambulation on the first to the third day (1945), with ambulation on the third to the seventh day (1946) and with supplemental use of position, exercises and circulatory stimulation. Usually 1 or 2 deaths from massive embolism occurred each year.

Thirteen cases of thromboembolism were encountered in patients permitted ambulation from the first to the third day postoperatively. One died from massive embolism on the fifth postoperative day. She had not been confined to bed preoperatively.

The preponderant incidence of the lesion in community surgery as indicated by this analysis is among the patients over fifty years of age, particularly after pelvic, gall-bladder or bowel surgery.

When Dicumarol was administered prophylactically (1948) to all patients not permitted ambulation on the first to the third day, the rate of thromboembolism dropped sharply to 1.5 per cent, with no deaths from embolism.

Bibliography

Allen, A. W., Linton, R. R., and Donaldson, G. A. Thrombosis and embolism: review of 202 patients treated by femoral vein interruption. *Ann. Surg.* **118**:728-740, 1943.

Idem. Venous thrombosis and pulmonary embolism: further experience with thrombectomy and femoral vein interruption. *J. A. M. A.* **128**:397-403, 1945.

Idem. Venous thrombosis and pulmonary embolism. *J. A. M. A.* **133**: 1268-1276, 1947.

Allen, E. V. Clinical use of anticoagulants: report of treatment with dicumarol in 1,686 postoperative cases. *J. A. M. A.* **134**:323-329, 1947.

Barker, N. W. Use of dicumarol in surgery. *Minnesota Med.* **27**:102-106, 1944.

Barker, N. W., Nygaard, K. K., Walters, W., and Priestly, J. T. Statistical study of postoperative venous thrombosis and pulmonary embolism: time of occurrence during postoperative period. *Proc. Staff Meet., Mayo Clin.* **16**:17-21, 1941.

Barnes, A. C., and Ervin, H. H. Effect of anticoagulants on post-partum bleeding. *Surg., Gynec. & Obst.* **82**:528-530, 1936.

Blodgett, J. B. Early ambulation following surgical procedures. *Bull. New York Acad. Med.* **25**:176-184, 1949.

Blodgett, J. B., and Beatie, E. J. Early postoperative rising: statistical study of hospital complications. *Surg., Gynec. & Obst.* **82**:485-489, 1946.

deTakats, G., and Fowler, E. Problem of thromboembolism. *Surgery* **17**: 153-177, 1945.

Faure, J. L. Discussion of Morice, M. A. Du traitement préventif des phlébites après hystérectomies pour fibromes par les autovaccins. *Bull. et mém. Soc. nat. de chir. de Paris* **53**:517-524, 1927.

Fine, J., and Starr, A. Surgical therapy of thrombosis of deep veins of lower extremities. *Surgery* **17**:232-239, 1945.

Frykholm, R. Pathogenesis and mechanical prophylaxis of venous thrombosis. *Surg., Gynec. & Obst.* **71**:307-312, 1940.

Leithauser, D. J., and Bergo, H. L. Early rising and ambulatory activity after operation: means of preventing complications. *Arch. Surg.* **42**:1086-1093,1941.

Potts, W. J., and Smith, S. Pulmonary embolism: experimental study of variations in volume blood flow in inferior vena cava of dog. *Arch. Surg.* **42**:661-664, 1941.

Rössle, R. Über die Bedeutung und die Entstehung der Wadenvenenthrombosen. *Virchows Arch. f. path. Anat.* **300**:180-189, 1937.

Smith, G. V., and Mulligan, W. G. Dicumarol prophylaxis against venous thrombosis in women undergoing surgery. *Surg., Gynec. & Obst.* **86**:461-464, 1948.

Wise, W. D., Loker, F. F., and Brambel, C. E. Effectiveness of dicumarol prophylaxis against thromboembolic complications following major surgery: four year survey: 3,304 cases. *Surg., Gynec. & Obst.* **88**: 486-494, 1949.

Zava, L. Sui vantaggi del levar precoce degli operati. *Policlinico (sez. prat.)* **47**:865-872, 1940.

DICUMAROL PROPHYLAXIS OF THROMBOEMBOLIC DISEASE IN CONGESTIVE HEART FAILURE*

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WITHIN the past decade the medical profession has become keenly aware of the danger of thromboembolic disease. First considered to be largely a postoperative complication, this condition is now realized to be actually more prevalent among medical patients.[1] Over half these patients suffer from heart disease, particularly congestive failure.[2]

Table 1. *Types of Heart Disease Encountered.*

Type of Heart Disease	Control Group	Dicumarol-Treated Group
	no. of patients	no. of patients
Hypertensive	26	24
Arteriosclerotic	41	27
Rheumatic	32	27
Miscellaneous	1	2
	100	80

Routine autopsies on patients in the middle to older age groups have revealed a rather staggering incidence of thrombosis. Rössle[3] and Hunter et al.[4] report an incidence of 27.0 and 52.7 per cent respectively of thrombophlebitis. These deep thrombi are without question responsible for the great majority of pulmonary emboli.

Why are patients with congestive heart failure liable to thromboembolic phenomena? There seem to be a number of contributing factors: bed confinement, stasis of blood in dependent edematous legs and perhaps damage to the venous endothelium from pressure and anoxia. In these patients the effect of the emboli is exaggerated by the already critical circulatory status. The mortality from emboli is appreciably greater in such patients than in patients without heart disease.[5]

In the management of thromboembolic disease the difficulty rests not so much with therapy as with diagnosis. Unfortunately, a serious hiatus exists between clinical ability to recognize thrombosis and embolism and its actual incidence as demonstrated by post-mortem examination. As it is only too clear from the present study, patients will die from thromboembolic disease despite close clinical surveillance. Prophylactic anticoagulant therapy seems to provide the only safeguard against this serious complication of congestive failure. The present study was undertaken to determine the safety of Dicumarol in this group of patients and its effectiveness in preventing thromboembolic disease.

Materials and Methods

During the past three years patients with congestive heart failure, irrespective of the heart disease, were placed on Dicumarol therapy or in a control group depending on whether their hospital admission was on an even or an odd day. Although this routine was adhered to in general, as the study progressed a greater number of patients were collected in the control group. Toward the end of the study all patients were placed on Dicumarol therapy to even the two groups numerically. The workup in the majority of patients included, in addition to routine studies, venous pressure, circulation time, vital capacity, heart film and fluoroscopy, and daily examination of the calves for possible signs of thrombophlebitis.

A group of 80 Dicumarol-treated patients and 100 control patients with congestive heart failure have been included in this study. The Dicumarol group represents 1725 hospital days, or an average

Table 2. *Evidence of Congestive Heart Failure.*

Group	Incidence of Dyspnea	Incidence of Rales	Incidence of Hilar Congestion	Incidence of Hydrothorax	Incidence of Cardiac Enlargement	Average Increase in Heart Size by X-Ray Examination	Incidence of Hepatomegaly	Incidence of Edema
	%	%	%	%	%	%	%	%
Control patients	99	88	91	57	96	32	80	80
Dicumarol-treated patients	99	89	92	56	98	35	76	80

*Normal, 50-150 mm.
†Arm-to-tongue method.

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of 22 days per patient. The control group represents 1914 patient hospital days, or an average of 19 days per patient. In the Dicumarol group 62 per cent were men, and 38 per cent women. In the control group there were 61 per cent men and 39 per cent women. The age distribution, type of heart disease and frequency of the manifestations of congestive failure in the two groups are shown in Tables 1, 2 and 3. The similarity of the two groups of patients is evident.

Only complications that were thought to occur during hospitalization were included. Patients with a history or physical findings of thromboembolic disease at the time of admission to the hospital were excluded from both series. In 2 cases unsuspected pulmonary emboli that antedated hospital admission were found at autopsy. In these cases, although the deaths were regarded as complications, the pulmonary emboli were not included since they did not occur during the period of hospitalization. Patients dying within forty-eight hours of admission and patients in failure because of an acute myocardial infarct were excluded from the study.

Table 3. *Age Distribution of Patients with Thromboembolic Complications.*

Decade	Control Group		Dicumarol-Treated Group	
	No. of patients	No. of complications	No. of patients	No. of complications
2nd	2	2	1	—
3rd	5	2	4	—
4th	17	4	15	—
5th	27	6	23	2
6th	28	3	19	2
7th	19	6	17	—
8th	7	—	1	—

Patients who were to receive Dicumarol had a prothrombin determination before the onset of therapy. During the first part of the study only patients whose prothrombin levels were above 60 per cent were used; later it was found that patients with lower levels could be safely treated. With an original prothrombin index of over 60 per cent, the initial dose of Dicumarol was 200 mg. An attempt was made to regulate prothrombin time at approximately 30 per cent. Prothrombin determination was performed according to Quick's method. A 20 per cent dilution was also made on each serum, and its prothrombin content determined. Daily prothrombin determinations were made throughout the period of Dicumarol therapy. Whenever there was evidence of thrombophlebitis or pulmonary embolism in the control group, prompt anticoagulant therapy was instituted.

Table 4. *Analysis of Complications.*

Group	Total No. of Deaths	Deaths Unrelated to Thromboembolic Disease	Cases of Thrombophlebitis	Cases of Pulmonary Embolism	Cases of Arterial Embolism
Control patients (100)	17 (17%)	8 (8%)	8 (8%)	15 (15%)†	1 (1%)
Dicumarol-treated patients (80)	7 (9%)	7 (9%)	2 (2.5%)*	2 (2.5%)†	1 (1%)

*One questionable case included.
†Two questionable cases included.

Results

Thromboembolic Complications and Deaths

In the control group of 100 patients there were 13 pulmonary emboli, 8 of which were proved at autopsy. In addition, 2 questionable cases were present. In the treated group of 80 patients only 2 questionable cases of pulmonary emboli occurred. Thrombophlebitis complicated 8 cases of the control series (4 demonstrated pathologically) as compared with 1 definite and 1 questionable case in the Dicumarol-treated group (Table 4).

There was a total mortality during hospitalization of 17 per cent in the control group and 9 per cent in the Dicumarol-treated group. It was of considerable interest that 8 of the deaths among the controls were believed, on the basis of the autopsy examination, to have been due to pulmonary embolism, whereas in the patients given Dicumarol none of the deaths were believed to

Table 2 (*Continued*).

Group	Incidence of Elevated Venous Pressure	Average Venous Pressure*	Incidence of Prolonged Circulation	Average Circulation Time†	Average Weight Lost in Hospital	Average Vital Capacity	Average Initial Prothrombin Time
	%	*mm. of saline solution*	%	*sec.*	*kg.*	*cc.*	%
Control patients	66	190	89	31	5.8	1500	77
Dicumarol-treated patients	67	192	87	31	5.0	1470	76

be due to embolism (Table 4). The chief causes of death in each group are listed in Table 5. It will be seen that the deaths unrelated to thromboembolic disease are quite similar in the two groups. Expressed as complications per 1000 hospital days

TABLE 5. *Analysis of Fatal Cases.*

CHIEF CAUSE OF DEATH	No. OF CONTROL CASES	No. OF DICUMAROL-TREATED CASES	AUTOPSIES	
			CONTROL CASES	DICUMAROL-TREATED CASES
Pulmonary embolism	8	—	8	—
Progressive heart failure	5	3	2	1
Aortic stenosis	2	2	2	2
Myocardial infarct	1	2	1	1
Rheumatic myocarditis	1		1	
Pulmonary embolism				

the same striking difference between the two groups is evident (Fig. 1).

In a review of the patients with thromboembolic complications in the control group, an average initial prothrombin determination of 91.4 per cent was found. In the remaining group of uncomplicated cases the average figure was 70 per cent.

Approximately half the patients in each group were on digitalis and the other half on Digitoxin.

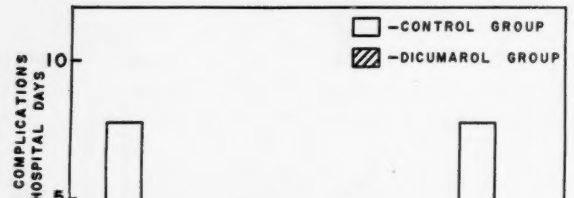

FIGURE 1. *Complications and Deaths among Control Group and among Patients Given Dicumarol.*

There was no correlation of the type of cardiac glycoside used with the occurrence of thromboembolic complication.

Dicumarol Administration

It was evident that some of the patients in the Dicumarol-treated group had serious liver dysfunction as shown by hepatomegaly, impaired bromsulfalein clearance and low prothrombin levels. It was anticipated that Dicumarol requirements might be rather small. The group of 80 treated patients required an average of 68 mg. per day. Prothrombin levels were kept at approximately 30 per cent — somewhat higher than is thought necessary in the treatment of thromboembolic disease. During the total period of hospitalization the prothrombin level of the Dicumarol-treated patients was below 50 per cent 71 per cent of the time, and below 30 per cent 55 per cent of the time. Under such conditions no serious difficulty from hemorrhage was encountered. There were 4 cases of minor bleeding, including epistaxis, hematuria, melena and hemoptysis. In no case was vitamin K_1 or blood transfusion necessary.

DISCUSSION

The therapeutic efficacy of Dicumarol in the treatment of thromboembolic disease has been well demonstrated. Recently, favorable reports of its prophylactic use in myocardial infarction and in congestive failure have been published.[6-8] Of particular interest is the co-operative clinic report of 800 cases of myocardial infarction in which there was a third less mortality in the treated group and half the thromboembolic manifestations. It would be of interest to know from this large series if patients with congestive heart failure in addition to myocardial infarction represented the key group receiving most benefit from anticoagulant therapy.[6] In 61 patients with congestive heart failure treated by Wishart and Chapman[7] the incidence of pulmonary emboli was 6.5 per cent, with only 1 death, which was questionably attributed to embolism. Sixty-one cases are also reported by Anderson and Hull[8] along with 58 controls. The mortality observed was 11 per cent in their treated group and 18 per cent in their control group. It appeared likely that 2 patients in the treated group died of embolism.

In the present study it is impressive that as the probable result of pulmonary embolism, 8 patients in the control group died as compared with none in the Dicumarol-treated group. The greater number of autopsies in the control group might appear to weight the series. However, the fact that these emboli appeared to be responsible for the patients' deaths is evidence against this. It is also likely that there would have been other deaths in the control series had not prompt treatment been instituted on the appearance of signs and symptoms of thromboembolic disease. When the complications are related to hospital days, essentially the same relations are maintained — that is, twice the mortality and five times the incidence of pulmonary embolism (Fig. 1).

The importance of the state of coagulability of the blood is indicated by the higher average prothrombin level in patients in whom thromboembolic disease developed. One might assume that a prothrombin level of less than 50 per cent, whether due to Dicumarol or occurring spontaneously,

would protect a patient against thromboembolic disease. In reviewing the data from this standpoint one finds a 4 per cent incidence of complications in the "protected" group and a 36.5 per cent incidence in the "unprotected" group. It has been our belief that in prophylaxis of thromboembolic disease, a prothrombin level of 30 to 50 per cent may be quite satisfactory. This increases the safety of prothrombin administration. Should serious hemorrhage occur, it should be pointed out that the only vitamin K preparations that are effective in causing a rapid return of prothrombin to normal are vitamin K_1 and K_1 oxide.[9]

Summary

One hundred and eighty patients with congestive heart failure were studied. Eighty received Dicumarol, and a control group of 100 did not. The groups were similar in types of heart disease, age distribution and severity of heart failure.

It is the impression from this study that Dicumarol can be safely administered to such a group of patients, provided the usual precautions are taken.

The mortality in the Dicumarol-treated group was approximately half that of the control group. The difference appeared to be due to the absence of fatal embolic complications in the former.

The data presented suggest that Dicumarol resulted in a significant reduction in thromboembolic disease and thus decreased the mortality in patients hospitalized with congestive failure.

References

1. Hampton, A. O., and Castleman, B. Correlation of postmortem chest teleroentgenograms with autopsy findings, with special reference to pulmonary embolism and infarction. *Am. J. Roentgenol.* **43**:305-326, 1940.
2. Carlotti, J., Hardy, I. B., Jr., Linton, R. R., and White, P. D. Pulmonary embolism in medical patients, comparison of incidence, diagnosis and effect of treatment in two hundred and seventy-three cases at Massachusetts General Hospital in two five-year periods (1936 to 1940 and 1941 to 1945 inclusive). *J. A. M. A.* **134**:1447-1452, 1947.
3. Rössle, R. Über die Bedeutung und die Entstehung der Wadenvenenthrombosen. *Virchows Arch. f. path. Anat.* **300**:180-189, 1937.
4. Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C. Thrombosis of deep veins of legs: its clinical significance as exemplified in 351 autopsies. *Arch. Int. Med.* **68**:1-17, 1941.
5. Krause, G. R., and Chester, E. M. Infarction of lung: clinical and roentgenologic study. *Arch. Int. Med.* **67**:1144-1156, 1941.
6. Wright, I. S., Marple, C. D., and Beck, D. F. Report of Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction. *Am. Heart J.* **36**:801-815, 1948.
7. Wishart, J. H., and Chapman, C. B. Dicumarol therapy in congestive heart failure. *New Eng. J. Med.* **239**:701-704, 1948.
8. Anderson, G. M., and Hull, E. Use of dicumarol as adjunct to treatment of congestive heart failure: results in controlled series of 61 cases. *South. M. J.* **41**:365-371, 1948.
9. Miller, R., Harvey, W. P., and Finch, C. A. Antagonism of dicumarol by vitamin K preparations. *New Eng. J. Med.* **242**:211-215, 1950.

ANTAGONISM OF DICUMAROL BY VITAMIN K PREPARATIONS*

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DICUMAROL is of proved value in the prophylaxis and treatment of thromboembolic disease. In recent years it has come into general clinical usage. The narrow margin between a clinically effective prothrombin level and the prothrombin level at which bleeding occurs imposes a certain hazard in treatment. Even with the most careful management of Dicumarol therapy, an unsuspected complication such as an asymptomatic peptic ulcer may result in fatal hemorrhage. The literature attests the seriousness of such bleeding in patients treated with Dicumarol.[1-4]

In event of hemorrhage it is of the utmost importance to *remedy quickly the coagulation defect* produced by Dicumarol. The two measures recommended for this purpose are the administration of vitamin K preparations and blood transfusion. The literature suggests that synthetic vitamin K preparations are effective when given intravenously in large doses.[5-7] The recent observations of James et al.[8] and our personal experience in the treatment of patients cast doubt on this. Accordingly, the potency of various vitamin K preparations in antagonizing the action of Dicumarol was studied in animals and man under controlled conditions.

Materials and Methods

Dicumarol dissolved in alkaline solution was administered intraperitoneally in rats and intravenously in dogs. In the animal experiments the parenteral route was chosen to exclude possible variations in intestinal absorption. In human subjects the Dicumarol was administered by mouth. The following vitamin K preparations¶ were assayed: vitamin K_1 (2-methyl-3 phytyl-1, 4-naphthoquinone), vitamin K_1 oxide, menadione (2 methyl-1, 4 naphthoquinone), menadione bisulfite (Hykinone) and Synkayvite (2-methyl-1, 4 naphthohydroquinone diphosphoric ester tetra-sodium salt).

The prothrombic activity was determined by the one-stage method of Quick.‖ Daily control bloods were drawn from a single normal dog for the data

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¶These various preparations were kindly supplied by the following companies: vitamin K_1 and K_1 oxide by Merck and Company, Incorporated, Rahway, New Jersey; menadione by Eli Lilly Research Laboratories, Indianapolis, Indiana; Hykinone by Abbott Research Laboratories, North Chicago, Illinois; and Synkayvite by Hoffmann-LaRoche, Incorporated, Nutley, New Jersey.

‖Thromboplastin was kindly supplied by the Maltine Company.

reported on animals in Table 1 and from 1 of 4 normal volunteers for the clinical studies (Table 2). Prothrombin times are expressed both in seconds and in percentage. In addition to the undiluted sulfate in dog and Seitz filtered plasma in human studies.

In experiments using rats, groups of 4 animals were given intraperitoneal injections of either 5

TABLE 1. *Effect of Vitamin K Preparations on Dicumarol-Induced Hypoprothrombinemia in Dogs.**

Vitamin Preparation	Amount	Prothrombin Time					Prothrombin Time				
		Initial	4-hr.	8-hr.	24-hr.	48-hr.	Initial	4-hr.	8-hr.	24-hr.	48-hr.
	mg.	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	*%*	*%*	*%*	*%*	*%*
Intravenous administration:											
K_1	6	44.5	41.0	—	18.0	21.0	<5	<5	—	5–10	5–10
K_1	4	30.0	22.5	25.0	14.5	18.0	<5	<5	<5	10	5–10
K_1	60	22.0	—	11.5	8.0	8.0	5	—	20	60	60
K_1	60	25.5	—	12.0	7.8	8.0	<5	—	20	70	60
K_1 oxide	4	27.0	31.5	25.5	21.0	20.0	<5	<5	<5	5	5
K_1 oxide	4	50.0	61.0	55.5	51.0	63.0	<5	<5	<5	<5	<5
K_1 oxide	60	63.0	—	88.0	26.0	26.0	<5	—	<5	<5	<5
K_1 oxide	60	22.0	—	—	12.0	14.5	5	—	—	20	10
Hykinone	6	20.0	17.0	23.0	17.5	—	5	5–10	<5	5–10	—
Hykinone	60	36.0	—	—	32.0	44.5	<5	—	—	<5	<5
Hykinone	200	24.0	—	23.5	26.0	102.0	<5	—	—	<5	<5
Hykinone	200	32.0	—†	—†	38.5	27.0	<5	—	0	<5	<5
Hykinone	864	33.5	42.0	38.0	70.5	63.0	5	<5	<5	<5	<5
Hykinone	1000	20.0	21.0	17.0	21.0	22.0	5	5	5	5	5
Synkayvite	6	11.0	11.5	18.0	14.0	—	15	15	5–10	10	—
Synkayvite	60	45.0	46.0	59.0	66.0	72.5	<5	<5	<5	<5	<5
Synkayvite	200	46.5	78.0	76.0	240.0	87.5	<5	<5	<5	<5	<5
Oral administration:											
K_1	60	18.0	11.0	7.5	10.0	18.0	5–10	20	70	20	5–10
K_1	60	39.0	10.0	10.0	8.0	12.0	<5	20	20	60	15
K_1 oxide	60	24.0	33.0	30.5	18.5	20.0	5	<5	<5	5–10	5
K_1 oxide	60	72.5	70.0	70.0	46.5	46.5	<5	<5	<5	<5	<5
Hykinone	1000	19.0	22.0	26.0	28.0	23.0	5	5	<5	<5	<5
Synkayvite	1000	21.0	27.0	29.0	43.5	51.0	5	<5	<5	<5	<5
Menadione	1000	23.0	24.5	23.0	37.0	23.0	<5	<5	<5	<5	<5

*All dogs were maintained on 6 mg. of Dicumarol a day throughout the experimental period. The control prothrombin time was 7-8 sec.
†No clot.

prothrombin determinations, 20 per cent saline dilutions and 12.5 per cent dilutions with plasma treated with barium sulfate were also performed. These determinations, however, were consistent

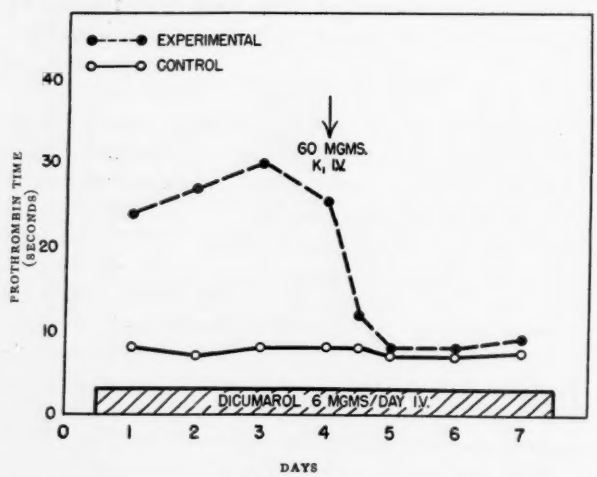

FIGURE 1. *Assay of Vitamin K Preparation in a Dog.*

with the undiluted prothrombin values and are therefore not included in the report. The prothrombin percentage was calculated from experimentally determined curves using plasma treatment barium or 20 mg. of Dicumarol in addition to amounts of vitamin K preparations varying from 1 to 50 mg. A single blood sample was drawn at twenty-four hours by cardiac puncture for determination of prothrombin times and compared with values obtained in normal animals.

The studies on dogs and man were designed to overcome possible criticism inherent in some previous reports. The animals and patients were maintained on a given dose of Dicumarol through the period of study. Reasonably stable prothrombin levels were obtained on the three days preceding the administration of vitamin K. The same dose of Dicumarol was continued daily after the injection of vitamin K. Thus, any appreciable change in prothrombin times could be attributed to the preparation assayed (Fig. 1). In the clinical studies a daily Dicumarol dose about 25 mg. in excess of the previous maintenance dose was employed.

In dogs the oral preparations were given in capsules or by stomach tube. Menadione was dissolved in cotton-seed oil and mixed with milk. All preparations with the exception of menadione were given intravenously to dogs. In man the compounds were given orally and intravenously, as indicated in Table 2. Vitamin K_1 and K_1 oxide were given by mouth in gelatin capsules. When given parenterally they were prepared as previously described[9] by dissolving in 1 to 4 cc. of ethyl alcohol, this mixture being added to 200 to 500 cc.

of 5 per cent glucose solution to form a fine colloidal suspension. Sterilization was accomplished by previous Seitz filtration. These preparations were given intravenously over a period of fifteen to thirty minutes. Since vitamin K_1 is light sensitive, precautions were taken to keep it from exposure to light during its preparation and administration. A certain amount of vitamin K_1 and a smaller amount of vitamin K_1 oxide precipitated on the sides of the flask, so that actual doses administered were somewhat smaller than the figures recorded in Tables 1 and 2.

Table 2. *Effect of Vitamin K Preparations on Dicumarol-Induced Hypoprothrombinemia in Man.*

Dicumarol Dosage	Vitamin Preparation	Amount	Prothrombin Time						Prothrombin Time				
			control	0-hr.	4-hr.	8-hr.	24-hr.	48-hr.	0-hr.	4-hr.	8-hr.	24-hr.	48-hr.
mg./day		*mg.*	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	%	%	%	%	%
Intravenous administration:													
50	K_1	500	15	29	23	22.0	16		20	30	35	90	
100	K_1	1000	16–17	32	25	20.0	17	17	20	35	45	100	95
150	K_1	1000	16–17	52	28	22.0	17	16	10	25	35	80	100
50	K_1 oxide	500	16–17	38	40	26.0	21		15	15	30	50	
75	K_1 oxide	1000	15–16	60	50	36.0	23	17	10	10	15	40	95
50	Hykinone	60	16	27	26	25.0	17		25	30	30	90	
150	Hykinone	250	15	60	62	61.0	41		10	10	10	10	
100	Hykinone	288	16	29	34	—	27		20	15		20	
100	Hykinone	1000	15	41	48	43.0	37		10	10	10	10	
75	Hykinone	64	10	28	32	31 (12 hr.)	31	26	20	18	19 (12 hr.)	18	21
50	Hykinone	64	10	25	28	28 (12 hr.)	24	18	22	20	20 (12 hr.)	23	30
Oral administration:													
50	K_1	500	15–17	25	27	20.0	16	17	30	25	60	90	100
50	K_1	1000	17	30	23	20.0	17		25	45	75	100	
100	K_1	1000	15–16	30	30	25.0	18	20	15	15	25	80	60
50	K_1 oxide	500	16	48	48	42.0	28		10	10	10	25	
50	K_1 oxide	1000	15–16	45	44	27.5	20	16	10	10	25	60	90
50	K_1 oxide	1000	15–16	31	29	24.0	19	17	15	20	30	30	90

Results

Results of studies on about 20 groups of 4 rats are briefly summarized. The intraperitoneal injection of 5 mg. of Dicumarol caused a prolongation of prothrombin time twenty-four hours later from the normal of 13 to 15 seconds to an average of 35 seconds. Five milligrams of vitamin K_1 or K_1 oxide, when injected intraperitoneally with the Dicumarol, reduced the prothrombin time to between 15 and 20 seconds. Water-soluble vitamin K preparations resulted in prothrombin times ranging from 19 to 35 seconds. It was of interest that increasing the amounts of these water soluble preparations (menadione bisulfite and Synkayvite) up to 50 mg. did not exert a greater effect than the 5 mg. When the dose of Dicumarol was increased to 20 mg., control rats died of pericardial hemorrhage. Rats given 5 to 20 mg. of vitamin K_1 and K_1 oxide survived and showed prothrombin times varying from 15 to 35 seconds. Rats given 20 mg. of Hykinone or Synkayvite usually died of pericardial hemorrhage or, if surviving, showed greatly prolonged prothrombin times.

More extensive studies were then performed on dogs (Table 1). A typical assay is shown in Figure 1. Both vitamin K_1 and K_1 oxide were effective in reducing prothrombin times in dogs maintained on Dicumarol. Vitamin K_1 appeared to be the more effective when given intravenously and, in doses of ten times the daily Dicumarol dose, brought the prothrombic activity of the blood to well above bleeding levels. In contrast to the above compounds, the vitamin K preparations without the phytyl side chain — that is, Hykinone, Synkayvite and menadione — in doses from 6 to 1000 mg. intravenously or by mouth had no demonstrable ability to lower the prothrombin time. Toxic manifestations were observed with doses of menadione bisulfite of 1000 mg. and with amounts of Synkayvite above 250 mg. Oral administrations of these compounds likewise showed definite activity by both vitamin K_1 and K_1 oxide but no effect with the other preparations. However, the prothrombin increase produced by vitamin K_1 and K_1 oxide orally was less marked and more transient than equivalent doses given intravenously.

It was possible to conduct the same type of assay clinically in patients receiving Dicumarol for prophylactic reasons. In Table 2 the dose of Dicumarol on which the patients were stabilized is recorded. The same dose was maintained after the vitamin K preparation had been given. Both vitamin K_1 and K_1 oxide were effective in doses of 500 to 1000 mg., and no toxic reactions were observed. Vitamin K_1 was more potent than vitamin K_1 oxide. In general, the water-soluble vitamin K preparations were without effect. Although 1 patient on 50 mg. of Dicumarol per day appeared to respond to intravenous injection of 60 mg. of menadione bisulfite, no definite response was observed in other patients given amounts of menadione bisulfite from 64 to 1000 mg. Oral administration of these compounds gave results comparable to previous observations in animals.

Discussion

Water-soluble synthetic vitamin K preparations have been referred to frequently in clinical articles as an effective means of counteracting Dicumarol

toxicity.[5-7] This is based on two types of evidence: the first is that these preparations are effective when very small amounts of the anticoagulant are given.[10, 11] Secondly, menadione bisulfite in many cases unquestionably accelerates the return of the prothrombin time to normal after Dicumarol has been stopped. This was clearly demonstrated by Cromer and Barker.[12] It is of interest that their patients had not received Dicumarol for twenty-four to forty-eight hours before the menadione bisulfite was given and also that the average prothrombin time did not appear to rise above 50 per cent for several days after the administration of the menadione bisulfite intravenously. Subsequent clinical observations suggest that the antagonistic effect of much larger doses of the same preparation was almost negligible, and certainly inadequate to meet the emergency of hemorrhage caused by Dicumarol.[8]

From the studies herein reported it is evident that, in animals maintained on Dicumarol, vitamin K_1 and K_1 oxide may effect a prompt return of prothrombin time toward normal. The same results were found in patients. A 1-gm. dose of vitamin K_1 intravenously was perhaps optimal in man and could be depended on to correct the hemorrhagic tendency within a matter of hours. This is consistent with the report of Davidson and MacDonald[13] and of Lucia and Aggeler.[14] In contrast to this, the water-soluble synthetic vitamin K preparations tested showed no antagonistic effect and at near toxic levels appeared in some cases to prolong the prothrombin time further. Any larger doses were prohibitive because of the toxicity of the compound used. A similar lack of antagonistic action of the water-soluble preparations was recently

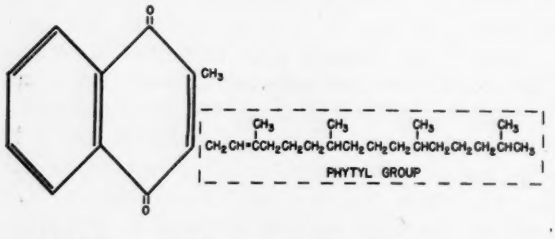

FIGURE 2. *Structure of Vitamin K_1.*

reported in rats with the use of the two-stage method of prothrombin determination.[15]

The discrepancy between this and previous reports indicating a positive action of the water-soluble vitamin K preparations may be explained, in part, by the smaller doses employed by some authors, for in our rats with coincidental administration of Dicumarol and water-soluble vitamin K preparations at lower doses some antagonistic effect was demonstrated. Likewise, the evidence cannot be questioned that menadione bisulfite accelerates the return of prothrombin to normal after Dicumarol has been discontinued for one or more days. This suggests that the effect of the water-soluble compounds is evident only after the bulk of the Dicumarol has been disposed of by the body.

The marked difference of various vitamin K preparations in their ability to antagonize the action of Dicumarol is in contrast to potency assays in vitamin-deficient birds or animals.[16] Such studies have shown a greater potency on the part of some of the water-soluble preparations, which were completely inactive in our experiments. This indicates that the phytyl chain (Fig. 2) is not a necessary part of vitamin K for prothrombin synthesis in an animal deficient in vitamin K. However, with large amounts of Dicumarol present, the phytyl group appears to be essential.

In the presence of hemorrhage from Dicumarol, it is often imperative to increase the prothrombin activity rapidly. This hemorrhagic complication occurs usually during the time when Dicumarol is being administered, a situation quite analogous to our experiments on animals and human subjects during the immediate period of vitamin K administration. As shown by the previous experiments, the administration of 1 gm. of vitamin K_1 intravenously within four to twenty-four hours corrects the bleeding tendency and has been observed to do so on our wards when actual bleeding has been present.

The effect of an injection of vitamin K_1 or K_1 oxide may last for one or two weeks as judged by an increased requirement for Dicumarol to keep the prothrombin time depressed. The maintenance dose of Dicumarol in 1 patient was increased from 100 mg. a day before K_1 was given to 300 mg. over a period of eight days after the administration of vitamin K_1. Should further anticoagulant therapy be indicated, it has proved more convenient to change to heparin.

The injection of these potent vitamin K_1 compounds may be hazardous in patients with thromboembolic disease. In escaping serious hemorrhage the patient may again be placed in danger of fatal embolism. In such a situation the use of blood transfusions may be preferable, for bleeding may be stopped while the prothrombin level remains low. On the basis of in vitro studies adequately preserved bank blood should be as effective as fresh blood in the treatment of the coagulation defect caused by Dicumarol.[17] At the present time, however, there is not adequate clinical evidence to substantiate this supposition.

SUMMARY

The antagonism of therapeutic amounts of Dicumarol by vitamin K preparations has been studied in animals and man. Under the conditions of the experiments water-soluble vitamin K prepara-

tions had no antagonistic effect. Vitamin K_1 and, to a lesser degree, vitamin K_1 oxide were very effective in decreasing the prothrombin time. On the basis of these and other clinical observations it is suggested that vitamin K_1 and K_1 oxide provide the only known effective means, except blood transfusion, of treating the bleeding emergency of Dicumarol toxicity.

References

1. Shlevin, E. L., and Lederer, M. Uncontrollable hemorrhage after dicoumarol therapy with autopsy findings. *Ann. Int. Med.* **21**: 332-342, 1944.
2. Evans, J. A. Dicumarol therapy in thrombotic emergencies. *New Eng. J. Med.* **230**:131-135, 1944.
3. Cahan, A. Hemorrhage and purpura caused by dicoumarin: report of case. *New Eng. J. Med.* **228**:820-822, 1943.
4. Rosenbloom, D., and Crane, J. J. Massive hematuria due to dicumarol overdosage. *J. A. M. A.* **132**:924, 1946.
5. Barker, N. W., Cromer, H. E., Hurn, M., and Waugh, J. M. Use of dicumarol in prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration. *Surgery* **17**:207-217, 1945.
6. Wright, I. S. Experiences with dicumarol (3, 3'methylene-bis-[4 hydroxycoumarin]) in treatment of coronary thrombosis with myocardial infarction. *Am. Heart J.* **32**:20-31, 1946.
7. Levan, J. B. Dicoumarol therapy. *Ann. Int. Med.* **25**:941-949, 1946.
8. James, D. Personal communication.
9. Davis, W. A., Frank, H. A., Hurwitz, A., and Seligman, A. M. Intravenous use of vitamin K_1 oxide. *Arch. Surg.* **46**:296-300, 1943.
10. Shapiro, S., Redish, M. H., and Campbell, H. A. Prothrombin studies. III. Effect of vitamin K upon hypoprothrombinemia induced by dicumarol in man. *Proc. Soc. Exper. Biol. & Med.* **52**:12-15, 1943.
11. Overman, R. S., Field, J. B., Baumann, C. A., and Link, K. P. Studies on hemorrhagic sweet clover disease. IX. Effect of diet and vitamin K on hypoprothrombinemia induced by 3,3'methylenebis (4-hydroxycoumarin) in rat. *J. Nutrition* **23**:589-602, 1942.
12. Cromer, H. E., Jr., and Barker, N. W. Effect of large doses of menadione bisulfite (synthetic vitamin K) on excessive hypoprothrombinemia induced by dicumarol. *Proc. Staff Meet., Mayo Clin.* **19**: 217-223, 1944.
13. Davidson, C. S., and MacDonald, H. Effect of vitamin K_1 oxide on hypoprothrombinemia induced by dicoumarol. *New Eng. J. Med.* **229**:353-355, 1943.
14. Lucia, S. P. and Aggeler, P. M. Treatment of dicoumarol-induced hypoprothrombinemic hemorrhage with vitamin K_1 oxide. *Proc. Soc. Exper. Biol. & Med.* **56**:36, 1944.
15. Boyd, E. J., and Warner, E. D. Effect of vitamin K on dicumarol-induced hypoprothrombinemia in rats. *J. Lab. & Clin. Med.* **33**: 1431-1437, 1948.
16. Almquist, H. J. Vitamin K. *Physiol. Rev.* **21**:194-216, 1941.
17. Quick, A. J. On constitution of prothrombin. *Am. J. Physiol.* **140**: 212-220, 1943.

CLINICAL NOTE

A VERNIER CALIPER FOR INTERPRETING ELECTROCARDIOGRAMS

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THE measurements required in the interpretation of electrocardiograms are frequently made with relative inexactness. Considerable time may be wasted until a complex or other feature is found that falls on a line from which it may be measured with some accuracy. Experienced cardiologists learn to estimate distances with a high degree of accuracy, but even they may be encumbered with such tools as magnifying lenses and rules and often with drafting calipers. Those who are less experienced frequently need to make certain computations, which, although not elaborate, introduce the possibility of error.

The illustrated device (Fig. 1) adapts, for electrocardiographic purposes, the well known principle of the vernier caliper, and with it required computations are readily performed. On the assumption that the recording rate is 25 mm. per second, each vertical millimeter between the jaws is read directly in tenths of millivolts; each horizontal increment of 2.5 mm. is read directly in tenths of seconds. The addition of the vernier to the time scale enables the cardiologist rapidly to measure to the hundredth of a second with considerable accuracy. Since the first two increments on the time scale, 0.1 and 0.2 second, represent the acceptable upper limits for normal QRS complexes and PR intervals respectively, normal limits for these data are readily verified.

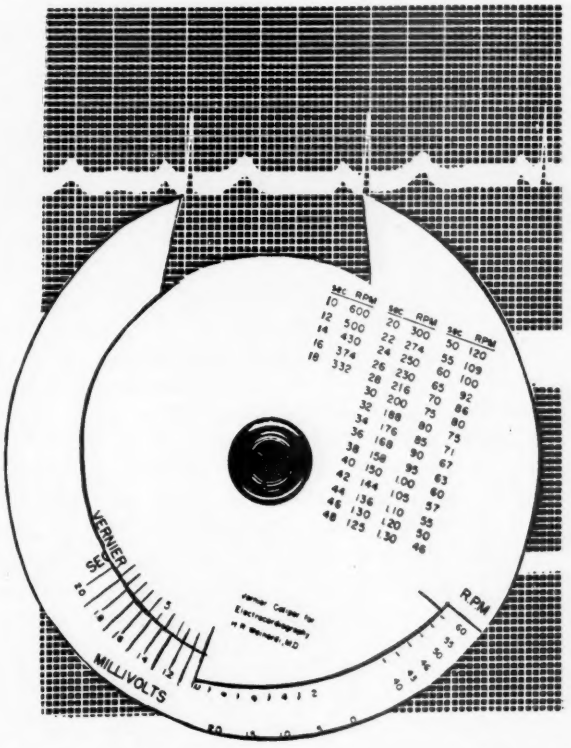

FIGURE 1. *Application of the Caliper to Analogous Parts of Successive Complexes, Indicating on the Scale* (R. P. M.) *a Rate of 60 per Minute.*

The apical rate is ascertained with equal facility if the jaws of the caliper are applied to analogous

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positions on successive complexes and is then read directly on the rate-per-minute scale. By adjusting the jaws in this manner and applying them to a series of complexes, the cardiologist can detect even small variations in the duration of the cardiac cycle. The usefulness of the rate-per-minute scale is further enhanced by the table incorporated on the caliper.

This vernier caliper for interpreting electrocardiograms was designed with particular emphasis on simplicity of operation and of manufacture. We prepared the illustrated model by reducing a large scale drawing and reproducing it directly on a plastic material coated with a photographic emulsion. It could be produced with much greater precision by persons accustomed to the manufacture of such scales and should be very inexpensive. Because they can be made so inexpensively, calipers calibrated for other paper speeds may easily be prepared. If the central rivet were made larger it might also embrace a small magnifying lens and still permit motion of the two leaves. This would make it more complete but also more expensive. The present model weighs exactly 2 gm. and is 7.6 cm. in diameter.

Summary

A convenient and versatile vernier caliper has been designed by which calculations of interest to those interpreting electrocardiograms may readily be determined. It is small and light and may be so manufactured as to be inexpensive.

We are indebted to Professor Polykarp Kusch, of the Department of Physics, Columbia University, for advice and help.

MEDICAL PROGRESS

ANTICOAGULANTS (Concluded)*

Douglas S. Riggs, M.D.†

BOSTON

Dicumarol

In 1922 Schofield[44] described a hemorrhagic disease in cattle fed spoiled sweet-clover hay. Roderick[45] found that the basic defect in sweet-clover disease was prothrombin deficiency and that the hemorrhagic tendency could be controlled by a withdrawal of the diet of spoiled hay and transfusion of fresh blood from healthy cattle. In 1934 Link and his collaborators at the University of Wisconsin Agricultural Experiment Station initiated an intensive search for the causative agent in spoiled sweet clover. By 1940 the active principle had been isolated in crystalline form,[46] and shortly thereafter it was identified by synthesis as 3,3'-methylenebis (4-hydroxycoumarin), now known as Dicumarol.[47] The potential usefulness of the new compound as an anticoagulant was immediately recognized, and in 1941 the first clinical trial in 5 patients was reported by Butt, Allen and Bollmann.[48] Link[49] has given an absorbing account of the investigations that culminated in the synthesis of Dicumarol.

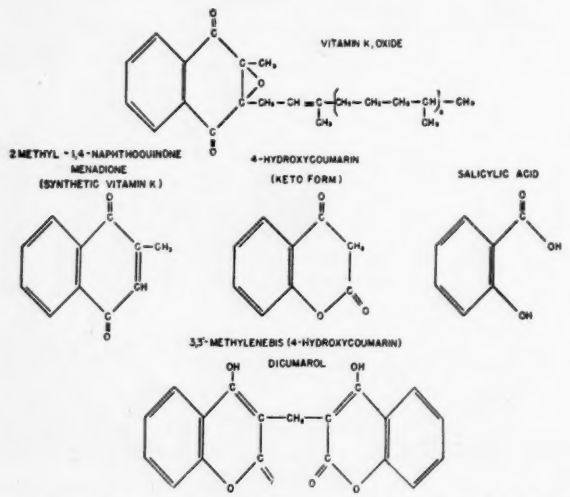

Figure 4. *Structural Formulas of Dicumarol and Related Compounds.*

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Chemistry

Dicumarol consists of two 4-hydroxycoumarin groups linked together by a CH_2 group. Keto-enol tautomerism can occur. The keto isomer of 4-hydroxycoumarin is illustrated in Figure 4 to emphasize its structural similarity to vitamin K and to salicylic acid. Dicumarol itself is poorly soluble in water, but with strong alkalies it forms salts that are soluble provided the pH of the solution is above 8.0. The compound is not very stable in such solutions.[50]

Many other coumarin derivatives have been examined for anticoagulant activity,[49, 51, 52] but none are as potent as Dicumarol itself. However, it is of considerable clinical importance that salicylic

acid, to which Dicumarol can be quantitatively degraded by vigorous treatment with alkali, may cause hypoprothrombinemia. Although the potency of acetylsalicylic acid is only about one twentieth that of Dicumarol,[53] doses of 2 gm. or more per day may produce a significant decrease of plasma prothrombin in man.[54]

Certain compounds not closely related to Dicumarol may exhibit similar biologic activity. Kabat and his co-workers[55] have reported that indandione derivatives can induce hypoprothrombinemia in animals. One of these, 2-pivalyl-1, 3-indandione, was as potent as Dicumarol.

Dicumarol is readily synthesized and is consequently inexpensive. It is available in tablets of 25, 50 and 100 mg.

Mechanism of Action

Dicumarol has no inhibitory action on blood clotting in vitro. Its anticoagulant effect is due chiefly, if not solely, to its suppression of prothrombin formation in the liver. Whereas heparin interferes with the reactions of coagulation, Dicumarol interferes with the manufacture of one of the reactants. This difference is fundamental and accounts for the total lack of similarity between the pharmacologic properties of heparin and Dicumarol.

The structural resemblance of 4-hydroxycoumarin to vitamin K (Fig. 4) led Woolley[56] to suggest that Dicumarol might act by competing with vitamin K in the reactions concerned with the synthesis of prothrombin. In favor of this hypothesis are the general similarity between the effects of vitamin K deprivation and Dicumarol administration, and the ability of vitamin K to reverse the action of Dicumarol in animals[57] and man.[58] However, certain observations are difficult to reconcile with the theory of simple competitive inhibition. Dam and Søndergaard[59] studied the prothrombin time of mixtures of plasma from chicks treated with Dicumarol or deficient in vitamin K. When plasmas from 2 chicks made hypoprothrombinemic by vitamin K restriction were mixed, the prothrombin time of the mixture always lay between the prothrombin times of the individual plasmas alone. The same limitation was true for mixtures of plasmas from Dicumarol-treated chicks. But when one plasma was from a chick deficient in vitamin K and the other from a chick treated with Dicumarol, a mixture of the two in certain proportions gave a prothrombin time somewhat *less* than that of either plasma alone. In no mixture, however, was the prothrombin time reduced to normal. These simple experiments demonstrate that although both vitamin K deficiency and Dicumarol impair prothrombin production, Dicumarol also produces a deficiency of some other clotting factor that is still present in the plasma of chicks deficient in vitamin K. Similar experiments in man suggest that the accessory clotting factor decreased by Dicumarol administration may be one of the proteins present in plasma or serum that accelerate the conversion of prothrombin to thrombin.[60-62]

The theory that Dicumarol acts competitively as a structural analogue of vitamin K also fails to explain the strictly limited ability of the vitamin to counteract the action of the anticoagulant. To nullify completely the effect of a given amount of Dicumarol in animals, much larger amounts of vitamin K are required.[57] Furthermore the ratio between the metabolite (vitamin K) and its analogue (Dicumarol) for a given degree of antagonism is not constant over a wide range of doses, as theory would demand.[56] These facts explain the inability of certain investigators to demonstrate any reversal of the Dicumarol effect by vitamin K in animals,[63] and the early reports that vitamin K was totally ineffective during Dicumarol treatment in man.[50] It is also noteworthy that the ability of 2,3-dichloro 1,4-naphthoquinone to inhibit the growth of yeast could be counteracted by the structurally similar synthetic vitamin K, menadione,[64] whereas the antibacterial action of Dicumarol in vitro could not.[65] However, since the dichloro analogue and Dicumarol were tested against different organisms, these results do not provide decisive evidence against the theory of competition.

Although the hypothesis that Dicumarol acts by competing with vitamin K is largely based on inference and analogy and lacks solid proof, the alternative theory that Dicumarol is "toxic" to the liver[13] is even more tenuous and far less attractive. Certainly Dicumarol impairs *a* liver function, but there is no substantial evidence that it produces any specific morphologic changes, either gross or microscopical,[66, 67] or that other functions of the liver are characteristically impaired.[50] To be sure, Irish and Jaques[68] reported that in dogs small doses of Dicumarol caused a rise in fibrinogen that was followed by a decrease to or below normal when the dose was increased, and they interpreted their results as evidence of a toxic action on the liver. However, no such action has been reported in man.[69] The available evidence indicates that Dicumarol in therapeutic doses produces a rather specific biochemical lesion and not the more diffuse sort of damage usually implied by such terms as "toxic action" and "liver poison."

Dicumarol has no effect on the platelet count, but a significant decrease in platelet adhesiveness has been observed in blood drawn from rabbits[70] and human subjects[71] with hypoprothrombinemia due to Dicumarol administration. The change is small, and it is doubtful whether it plays any major role in the prevention of thrombosis by Dicumarol.

Pharmacologic Properties

Dicumarol is readily absorbed from the gastrointestinal tract although a small portion may appear unchanged in the feces.[72] Little is known

of its distribution or fate. Only traces could be found spectrographically in the blood of rabbits twenty to twenty-four hours after intravenous administration.[53] No Dicumarol could be demonstrated by extraction or bioassay in the urine of dogs given 400 mg. per day for six days.[72] This is surprising since after nephrectomy[73] or kidney damage[74] the effect of a single dose of Dicumarol in animals is greatly prolonged, and patients with impaired renal function are abnormally sensitive to Dicumarol. Link has suggested that Dicumarol may be oxidized to salicylic acid in vivo as well as in vitro, but neither his group[49] nor Lester[75]

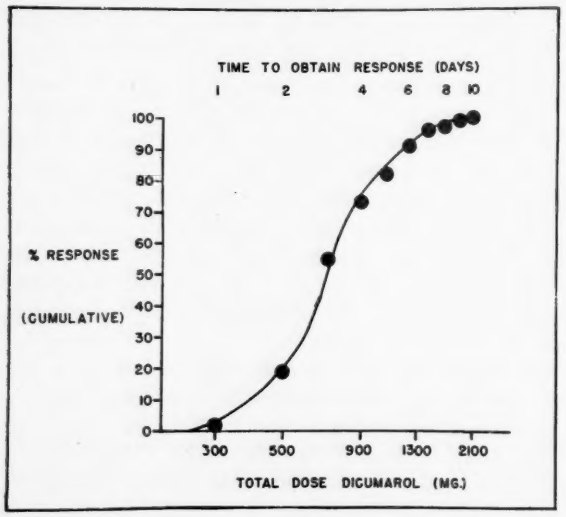

FIGURE 5. *Variations in Sensitivity to Dicumarol.*
Per cent responses were calculated from data given by James et al.,[77] the response being decrease of prothrombin activity to or below 20 per cent of normal. The sigmoid curve is symmetrical about the dose (approximately 700 mg.) that would elicit this response from half the patients.

could detect salicylates in the urine after the administration of Dicumarol.

The time of action of Dicumarol is of the utmost clinical importance. After a single dose the maximum effect is not attained for two or three days. The decrease of plasma prothrombin cannot be hastened beyond a certain limiting rate even by very large doses,[76] and the delay in attaining peak action probably represents the time needed for the stores of prothrombin present in the body to be exhausted. However, the size of the dose determines the maximum decrease of prothrombin attained and the duration of action. With clinically effective doses the prothrombin concentration usually does not approach normal for a week to ten days after administration of the drug has been discontinued, but the duration of action varies greatly from patient to patient.[77] It should be obvious that daily administration of Dicumarol will lead to cumulative action.

Variations in Sensitivity to Dicumarol

Early in their work, Link and his co-workers[49] were impressed by the great variations in sensitivity to Dicumarol among animals of the same species. They were able to show that in rabbits, susceptibility to Dicumarol was in part a hereditary characteristic.[49] Although a hereditary background has not been demonstrated for man, variations in sensitivity from patient to patient are quite as striking as in other species. James and his associates[77] have studied the amount of Dicumarol needed to reduce prothrombin activity* to 20 per cent of normal in 101 medical patients given 300 mg. the first day and 200 mg. daily thereafter. Their results have been plotted in Figure 5 in the form of a dose-response curve. This mode of expressing the results is not strictly justified because the number of days during which the total dose was given varied from patient to patient. However, it serves to emphasize the wide range of sensitivity observed in clinical practice.

Mode of Administration

Dicumarol is administered orally. Clinical studies, particularly those at the Mayo Clinic,[78] have established that thrombosis seldom occurs if prothrombin activity is less than 30 per cent of normal and that hemorrhage seldom occurs if prothrombin activity is greater than 10 per cent of normal. The therapeutic objective of maintaining the prothrombin activity within these limits can be achieved only by variation of the dose of Dicumarol to fit the response of the individual patient. Ordinarily 300 mg. is a safe initial dose. Thereafter, *it is imperative to adjust the dose according to the prothrombin activity determined once each day.* If the prothrombin activity is greater than 20 per cent, 100 to 200 mg. is given. If it is less than 20 per cent none is given. However, some attention must also be paid to the rate of change of prothrombin. If, for example, it is falling rapidly but has not yet reached 20 per cent it would be injudicious to give more.[79] Furthermore, if the patient is unusually sensitive or unusually resistant, the daily dose may need to be less than 100 or more than 200 mg. Indeed it is impossible to give any hard and fast rules for administering Dicumarol; the proper dosage schedule must be determined for each patient by a system of intelligent trial and error.

Since the effectiveness and safety of Dicumarol treatment are wholly dependent upon reliable prothrombin estimations it is most unfortunate that the determination and interpretation of prothrombin times differ widely from clinic to clinic. The one-stage method of Quick,[80] or some modification thereof, has been most extensively used. In this technic oxalated plasma is allowed to react

*Since factors other than prothrombin may affect the prothrombin time as usually determined, it is probably better to speak of "prothrombin activity" rather than "prothrombin concentration."

with optimal concentrations of thromboplastin and calcium, and the time needed for clot formation is measured. Because preparations of thromboplastin may differ in potency,[81, 82] it is essential to test each new preparation on several normal plasmas. Moreover, the relation between prothrombin *time* and prothrombin *concentration* is far from linear (Fig. 6). A curve relating the two variables should be determined in each laboratory for each batch of thromboplastin by measurement of the prothrombin times for various prothrombin concentrations obtained by dilution of normal plasmas with saline solution or with prothrombin-free plasma. From such a curve unknown plasmas can be read and reported in terms of percentage of normal. This mode of expressing the results tends to eliminate differences due to variations in thromboplastin and facilitates accurate regulation of Dicumarol dosage.[79]

Far worse than reporting results simply as prothrombin time is the completely misleading but apparently very widespread practice of calculating "percentage of prothrombin" by division of the prothrombin *time* for normal plasma by the prothrombin *time* for the unknown sample, the result being multiplied by 100. This mode of calculation is based on the erroneous assumption that if the prothrombin concentration is halved, the prothrombin time is doubled. It grossly overestimates prothrombin activity, and when used as a guide in attempts to maintain prothrombin between 10 and 30 per cent of normal, may lead to serious overdosage.[83]

Link[49] insists that the Quick method is too insensitive to give reliable results and vigorously supports the use of plasma diluted 1:8 with saline solution. Although it is true that Quick's method may fail to detect small decreases in prothrombin activity, these are not usually of clinical significance. In the range below 30 per cent of normal, most investigators have found the Quick procedure entirely adequate, whereas in the same range the end-point with Link's 12.5 per cent plasma is difficult to determine.

In the "two-stage" method of Smith and his co-workers[84] the prothrombin is completely converted to thrombin after the removal of fibrinogen. The time needed for formation of a clot in a specially prepared solution of fibrinogen is then measured. Although this method eliminates variability due to differences in the rate of thrombin formation, and therefore provides a more exact estimate of the actual concentration of prothrombin, the technic required is too intricate and takes too much time for general use. Furthermore, alterations in rate of thrombin formation may actually be caused by Dicumarol and may help to determine its clinical effect. In a detailed comparison of prothrombin methods used for controlling Dicumarol therapy Olwin[85] found the least day-to-day variation in prothrombin activity by the two-stage method, but he also stated that "the one-stage method is of value in estimating the summation of the various clotting factors."

The so-called "bedside method" for prothrombin determination is much too unreliable for use in control of Dicumarol administration,[80, 83] and at present Dicumarol cannot be safely employed unless the facilities of a properly equipped clinical laboratory are available.[86]

Toxicity

On intravenous injection, the LD_{50} of Dicumarol for various animals is about 50 mg. per kilogram of body weight. Death occurs within a few hours before any change in prothrombin can take place. By the oral route the LD_{50} is much larger, and death is delayed for several days.[87] The acute toxicity of Dicumarol is therefore low. But the daily administration of doses far smaller than the LD_{50} will eventually lead to death from hemorrhage. Since bleeding may not become evident until the prothrombin concentration has been dangerously low for some days, Link[49] has suggested that Dicumarol, in addition to impairing blood coagulation, may produce vascular damage. In support of this idea,

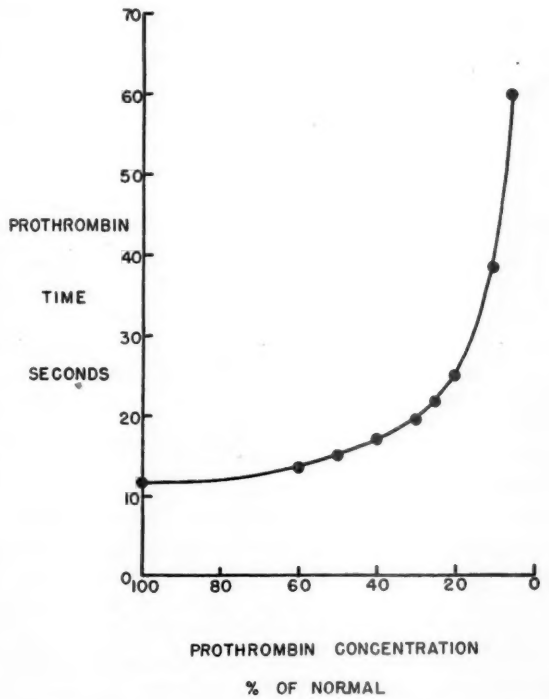

FIGURE 6. *Relation between Prothrombin Time and Prothrombin Concentration.*

The points have been plotted from the data of Quick.[3] The origin and shape of the curve vary with different preparations of thromboplastin. A standard curve of the type illustrated should be prepared whenever a new batch of thromboplastin is used, or the method of prothrombin determination is changed.

McCarter et al.[67] have found widespread dilatation of blood vessels and degenerative lesions of their walls in dogs poisoned with Dicumarol. However, no such changes were seen in dogs or human beings given therapeutic doses,[67] and capillary fragility is not increased during properly controlled administration of Dicumarol.[88]

Contrary to earlier statements, the erythrocyte sedimentation rate is not affected by the administration of either Dicumarol or heparin.[89]

Clinical Use of Anticoagulants

The objective of therapy with the anticoagulant drugs is to prevent the formation and growth of intravascular clots. Treatment must be continuous until the danger of thrombosis is past — usually until the patient is able to be up and about. Neither heparin nor Dicumarol will dissolve thrombi that are already present. However, by preventing further extension they may favor the recanalization of thrombosed vessels and the development of an adequate collateral circulation.[41]

It is not the purpose of this review to discuss in detail all the conditions amenable to treatment with heparin and Dicumarol. Only the commonest uses are mentioned in the following paragraphs.

Prophylactic Treatment

In the past venous thrombosis developed postoperatively in almost 1 per cent of surgical patients, and about 0.2 per cent died of pulmonary embolism.[13, 90] The incidence of thromboembolic disease among patients on medical wards was equally great.[91] Prophylactic exercises and early ambulation have reduced the prevalence of, but have by no means eliminated, venous thrombosis.[13] To treat every bed-ridden patient with anticoagulants would impose an impossible burden on the hospital and laboratory staff, and would subject many patients unnecessarily to the risk of bleeding. Some selection of patients for prophylactic treatment is essential. Unfortunately, none of the various tests proposed for the detection of a thrombotic tendency have proved reliable,[92] and selection must be based largely on an evaluation of factors known to favor the development of intravascular clotting. Lillie and his co-workers[91] have recently discussed indications for the prophylactic use of Dicumarol.

Table 1. *Outstanding Characteristics of Heparin and Dicumarol.*

Anticoagulant	Source	Chemical Nature	Mechanism of Action	Counteracting Agent	Route of Administration	Available Form	Approximate Dosage	Time of Action*			Control of Effect	Approximate Cost of 1 Day's Treatment
								Onset	Peak	Duration		
Heparin	Beef lungs (mast cells)	Highly acidic polysaccharide similar to mucoitin sulfuric acid	Inhibits conversion of prothrombin to thrombin (works in vivo and in vitro)	Protamine sulfate or toluidine blue (1-3 mg. per kilogram of body weight intravenously)	Intravenous or intramuscular	Heparin sodium; solution, 10 mg. (1000 units) per cubic centimeter	300 mg. per day	Immediate	10 min.	Usually less than 3 hr.	Maintain clotting time two or three times normal	$12
Dicumarol	Synthetic (spoiled sweet clover)	3,3′-methylenebis (4-hydroxycoumarin)	Inhibits prothrombin synthesis in liver (in vivo only)	Transfusions of fresh blood or plasma; menadione sodium bisulfite (50-100 mg. intravenously); vitamin K_1 oxide.	Oral	Dicumarol tablets (25, 50 and 100 mg.)	300 mg. initially; 0-200 mg. per day as needed.	Slow	2-3 days	About 10 days	Maintain prothrombin activity between 10 and 30 per cent of normal	A few cents

*After a single dose of heparin by vein or Dicumarol by mouth.

Treatment of Venous Thrombosis and Pulmonary Embolism

When peripheral venous thrombosis has already occurred, treatment becomes mandatory because of the grave danger of embolism. The prompt administration of anticoagulants has been at least as effective as venous ligation in preventing pulmonary infarcts and avoids the peripheral edema that sometimes follows interruption of the superficial femoral veins.[13] Even when a pulmonary embolus is the first sign of thrombosis it is not too late to institute treatment with anticoagulants, since the occurrence of subsequent emboli can usually be prevented.[93] However, venous ligation will continue to be useful when anticoagulants are contraindicated.

Coronary Thrombosis with Myocardial Infarction

In 1946 a special committee of the American Heart Association sponsored a co-operative study of the use of anticoagulant drugs in coronary occlusion with myocardial infarction. The results of this very carefully controlled investigation were unequivocally favorable.[94] Secondary myocardial infarctions, peripheral venous thromboses, pulmonary emboli and arterial emboli were all significantly less frequent among the 432 patients treated with anticoagulants than among the 368 untreated controls. The mortality was reduced from 24 to 15 per cent. Significant benefit was observed in all age groups and was still evident as late as four weeks after the original infarct. The conclusion that "Anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists" is amply justified. The idea that hemorrhage in the infarcted area might be increased by the administration of heparin or Dicumarol has been disproved by experiments in dogs.[95, 96]

Contraindications

Under certain circumstances the danger of bleeding outweighs the danger of thrombosis. Anticoagulants should obviously not be used in patients with a hemorrhagic tendency, nor in those with open wounds or ulcerations particularly of the gastrointestinal tract. Since even a small amount of bleeding in the central nervous system may be disastrous, anticoagulants are contraindicated after recent operations on the brain or spinal cord and after cerebrovascular accidents. In subacute bacterial endocarditis the danger of bleeding around a septic infarct in the central nervous system precludes the use of anticoagulant drugs. In patients with severe hypertension treatment is hazardous because of the danger of a cerebrovascular accident.

Other contraindications apply particularly to Dicumarol. It should be used with extreme caution, if at all, in hepatic damage because the synthesis of prothrombin may already be impaired, and in kidney disease because the duration of action is greatly prolonged. An absolute contraindication to the use of Dicumarol is lack of adequate facilities for the estimation of prothrombin.

Kraus, Perlow, and Singer[97] found that if the prothrombin activity of pregnant rabbits was reduced to below 10 per cent of normal by the administration of Dicumarol, fetal death from hemorrhage in utero would occur. Furthermore, Quick[98] has shown that when puppies are born of Dicumarol-treated bitches the prothrombin activity in the young is much lower than in the mother. These observations enjoin caution in the use of Dicumarol during pregnancy. On the other hand, properly controlled treatment with anticoagulants after delivery may not increase post-partum bleeding even when the first dose of Dicumarol is given during labor.[99] The occurrence of hypoprothrombinemia in the suckling young of rats fed Dicumarol suggests that it may be unwise to allow breast feeding while the mother is receiving the drug unless the infant is adequately protected with vitamin K.[100]

Control of Hemorrhage during Treatment

If bleeding occurs during the administration of heparin it can be promptly controlled by the slow intravenous injection of protamine sulfate or toluidine blue in a dose of 1 to 3 mg. per kilogram of body weight. When a repository preparation of heparin has been used, repeated injections may be needed,[101] or the antidote may be given by continuous infusion.

Even with meticulous control of the prothrombin level, bleeding must be expected in a small proportion of patients given effective doses of Dicumarol. At the Mayo Clinic[93] minor bleeding in the form of epistaxis, hematuria, petechiae and ecchymosis appeared in about 3.5 per cent of the patients, whereas major hemorrhage, chiefly from operative wounds, occurred in about 2 per cent. The incidence of major bleeding is lower among medical patients. Satisfactory control of hemorrhage may usually be achieved by transfusions of *fresh* whole blood or plasma. Lyophilized plasma may also be effective,[102] but blood or plasma stored in the fluid state is unsatisfactory because of loss of prothrombin activity. Large doses (50 to 100 mg.) of menadione sodium bisulfite or a similar water-soluble preparation of vitamin K injected intravenously will usually cause a return of prothrombin activity to safe levels within twenty-four hours.[58] Administration of vitamin K may be repeated every two to four hours until bleeding ceases. Vitamin K_1 oxide (Fig. 4) is said to have a more sustained effect. It must be dissolved in alcohol and emulsified in a 10 per cent glucose solution for intravenous administration. Doses as large as 2.0 gm. have been used.[77]

When the anticoagulant agents are properly used, death from hemorrhage is exceedingly rare. Many of the fatal cases reported[103] have been due to the grossest neglect of essential precautions.

Choice of Drug

Since heparin and Dicumarol are equally effective in the treatment of thrombosis, the choice between them is governed by their pharmacologic peculiarities. Heparin is the safer drug, but is not so convenient as Dicumarol for continued administration. Because of its evanescent action and ease of control, heparin is the agent of choice when anticoagulants are needed during and immediately after operations on blood vessels. The long latent period before Dicumarol becomes effective makes it imperative to use heparin whenever an immediate

action is required, as in pulmonary or arterial embolism.

It is often desirable to start treatment with heparin and Dicumarol simultaneously. Heparin may then be discontinued as soon as a satisfactory reduction of prothrombin activity has been achieved. Moderate prolongation of the clotting time with heparin does not seriously interfere with the determination of prothrombin,[104] but when large single doses are given intravenously, the prothrombin time may be prolonged. To avoid underestimating prothrombin activity, it is necessary to draw blood for the determination of prothrombin at least three hours after an intravenous injection of heparin.

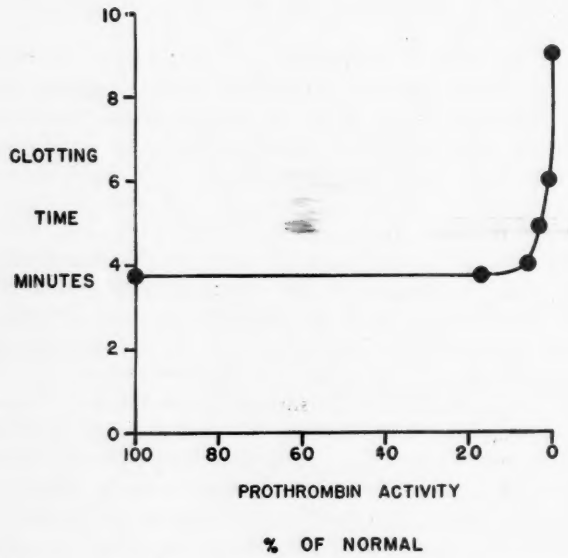

FIGURE 7. *Relation between Prothrombin Activity and Clotting Time.*

The points have been plotted from data obtained in experiments on dogs by Quick.[76] *There is little elevation in clotting time until the prothrombin activity is markedly reduced.*

The clotting time of blood is scarcely affected by Dicumarol administration until prothrombin activity falls far below normal[76] (Fig. 7). The clotting time may therefore be relied upon for controlling therapy with heparin until Dicumarol becomes effective.

SUMMARY

Certain outstanding characteristics of heparin and Dicumarol are summarized in Table 1. Neither drug is ideal. Perhaps an anticoagulant will eventually be found that will combine the best qualities of each. Until then, the physician may be thankful to have at his command two agents so different that they are collaborators, rather than rivals, in the treatment of thromboembolic disease. He may also be thankful for the work of such men as Howell, Best, Jorpes, Link and their associates, whose fundamental chemical and pharmacologic investigations made possible the safe and effective clinical use of heparin and Dicumarol.

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REFERENCES

44. Schofield, F. W. Brief account of disease in cattle simulating hemorrhagic septicaemia due to feeding sweet clover. *Canad. Vet. Rec.* **3**:74, 1922.
45. Roderick, L. M. Problem in coagulation of blood: "sweet clover disease of cattle." *Am. J. Physiol.* **96**:413-425, 1931.
46. Campbell, H. A., Roberts, W. L., Smith, W. K., and Link, K. P. Studies on hemorrhagic sweet clover disease. I. Preparation of hemorrhagic concentrates. *J. Biol. Chem.* **136**:47-55, 1940.
47. Stahmann, M. A., Huebner, C. F., and Link, K. P. Studies on hemorrhagic sweet clover disease. V. Identification and synthesis of hemorrhagic agent. *J. Biol. Chem.* **138**:513-527, 1941.
48. Butt, H. R., Allen, E. V., and Bollmann, J. L. Preparation from spoiled sweet clover (3,3′-methylenebis [4-hydroxycoumarin]) which prolongs coagulation and prothrombin time of blood: preliminary reports of experimental and clinical studies. *Proc. Staff Meet., Mayo Clin.* **16**:388-395, 1941.
49. Link, K. P. Anticoagulant from spoiled sweet clover hay. *Harvey Lectures* **39**:162-216, 1944.
50. Quick, A. J. Anticoagulants effective in vivo with special reference to heparin and dicumarol. *Physiol. Rev.* **24**:297-318, 1944.
51. Link, K. P. Anticoagulant 3, 3′-methylenebis (4-hydroxycoumarin). *Federation Proc.* **4**:176-182, 1945.
52. Lehmann, J. Effect of coumarin and dicoumarin derivatives on prothrombin level. *Lancet* **1**:458, 1943.
53. Link, K. P., Overman, R. S., Sullivan, W. R., Huebner, C. F., and Scheel, L. D. Studies on hemorrhagic sweet clover disease. XI. Hypoprothrombinemia in rat induced by salicylic acid. *J. Biol. Chem.* **147**:463-474, 1943.
54. Shapiro, S. Studies on prothrombin. VI. Effect of synthetic vitamin K on prothrombinopenia induced by salicylate in man. *J. A. M. A.* **125**:546-548, 1944.
55. Kabat, H., Stohlman, E. F., and Smith, M. I. Hypoprothrombinemia induced by administration of indandione derivatives. *J. Pharmacol. & Exper. Therap.* **80**:160-170, 1944.
56. Woolley, D. W. Recent advances in study of biological competition between structurally related compounds. *Physiol. Rev.* **27**: 308-333, 1947.
57. Overman, R. S., Field, J. B., Baumann, C. A., and Link, K. P. Studies on hemorrhagic sweet clover disease. IX. Effect of diet and vitamin K on hypoprothrombinemia induced by 3, 3′-methylenebis (4-hydroxycoumarin) in rat. *J. Nutrition* **23**:589-602, 1942.
58. Cromer, H. E., Jr., and Barker, N. W. Effect of large doses of menadione bisulfite (synthetic vitamin K) on excessive hypoprothrombinemia induced by dicumarol. *Proc. Staff. Meet., Mayo Clin.* **19**:217-223, 1944.
59. Dam, H., and Søndergaard, E. Observations on coagulation anomaly in vitamin K-deficiency and dicumarol poisoning. *Biochim. et Biophysika Acta* **2**:409-413, 1948.
60. Hurn, M., Barker, N. W., and Mann, F. D. Variations in prothrombin and antithrombin following administration of dicumarol. *Am. J. Clin. Path.* **17**:712-718, 1947.
61. MacMillan, R. L. Observations on mechanism of action of dicumarol. *Science* **108**:416, 1948.
62. Owen, C. A., and Bollmann, J. L. Prothrombin conversion factor of dicumarol plasma. *Proc. Soc. Exper. Biol. & Med.* **67**:231-234, 1948.
63. Boyd, E. J., and Warner, E. D. Effect of vitamin K on dicumarol-induced hypoprothrombinemia in rats. *J. Lab. & Clin. Med.* **33**: 1431-1437, 1948.
64. Woolley, D. W. Observations on antimicrobial action of 2,3-dichloro-1,4-naphthoquinone, and its reversal by vitamins K. *Proc. Soc. Exper. Biol. & Med.* **60**:225-228, 1945.
65. Goth, A. Antibacterial properties of dicumarol. *Science* **101**:383, 1945.
66. Emmel, V. M., and Dam, H. Absence of liver damage in chicks hypoprothrombinemic due to vitamin K deficiency or ingestion of 3, 3′-methylenebis (4-hydroxycoumarin). *Proc. Soc. Exper. Biol. & Med.* **56**:11-14, 1944.
67. McCarter, J. C., Bingham, J. B., and Meyer, O. O. Studies on hemorrhagic agent 3,3′-methylenebis (4-hydroxycoumarin). IV. Pathologic findings after administration of dicumarol. *Am. J. Path.* **20**:651-659, 1944.
68. Irish, U. D., and Jaques, L. B. Effect of dicumarol upon plasma fibrinogen. *Am. J. Physiol.* **143**:101-104, 1945.
69. Davidson, C. S., and MacDonald, H. Critical study of action of 3, 3′-methylenebis (4-hydroxycoumarin) (dicoumarin). *Am. J. M. Sc.* **205**:24-33, 1943.
70. Wright, H. P. Adhesiveness of blood platelets in rabbits treated with dicoumarol. *J. Path. & Bact.* **57**:382-385, 1945.
71. Spooner, M., and Meyer, O. O. Effect of dicumarol (3,3′-methylenebis [4-hydroxycoumarin]) on platelet adhesiveness. *Am. J. Physiol.* **142**:279-283, 1944.

72. Overman, R. S., et al. Studies on hemorrhagic sweet clover disease. VII. Effect of 3,3′-methylenebis (4-hydroxycoumarin) on prothrombin time of plasma of various animals. *J. Biol. Chem.* **142**: 941-955, 1942.
73. Richards, R. K., and Steggerda, F. R. Dicumarol (3,3′-methylenebis [4-hydroxycoumarin]) in rats with impaired liver or kidney function. *Proc. Soc. Exper. Biol. & Med.* **52**:358-360, 1943.
74. Bollman, J. L., and Preston, F. W. Effect of experimental administration of dicoumarin: 3,3′methylenebis (4-hydroxycoumarin). *J. A. M. A.* **120**:1021-1024, 1942.
75. Lester, D. Non-appearance of salicylates in urine after administration of dicumarol. *J. Biol. Chem.* **154**:305, 1944.
76. Quick, A. J. Experimentally induced changes in prothrombin level of blood. I. Quantitative studies in dogs given dicumarol. II. Effect of methylxanthines on prothrombin per se and when administered with dicumarol. *J. Biol. Chem.* **161**:33-44, 1945.
77. James, D. F., Bennett, I. L., Jr., Scheinberg, P., and Butler, J. J. Clinical studies on dicumarol hypoprothrombinemia and vitamin K preparations. I. Superiority of vitamin K1 oxide over menadione sodium bisulfite U.S.P. and synkayvite in reversing dicumarol hypoprothrombinemia. *Arch. Int. Med.* **83**:632-652, 1949.
78. Barker, N. W., Cromer, H. E., Hurn, M., and Waugh, J. M. Use of dicumarol in prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration. *Surgery* **17**:207-217, 1945.
79. Allen, E. V. Clinical use of anticoagulants: report of treatment with dicumarol in 1,686 postoperative cases. *J. A. M. A.* **134**: 323-329, 1947.
80. Quick, A. J. On quantitative estimation of prothrombin. *Am. J. Clin. Path.* **15**:560-566, 1945.
81. Hurn, M., Barker, N. W., and Magath, T. B. Prothrombin time determinations following administration of dicumarol, with special reference to variability of thromboplastin. *Proc. Staff Meet., Mayo Clin.* **19**:507-512, 1944.
82. Conley, C. L., Morse, W. I. II, and Stewart, E. E. Thromboplastic factors in estimation of prothrombin concentration. *Am. J. M. Sc.* **215**:158-169, 1948.
83. Rivers, D. C. "Dicumarol" and prothrombin. *J. A. M. A.* **137**: 666, 1948.
84. Warner, E. D., Brinkhous, K. M., and Smith, H. P. Quantitative study on blood clotting: prothrombin fluctuations under experimental conditions. *Am. J. Physiol.* **114**:667-675, 1936.
85. Olwin, J. H. One-stage and two-stage prothrombin methods in control of dicumarol therapy, with remarks on ac-globulin. *J. Lab. & Clin. Med.* **34**:806-812, 1949.
86. Wright, I. S. Value of prothrombin determinations. In *Blood Clotting and Allied Problems.*[3] P. 96.
87. Rose, C. L., Harris, P. N., and Chen, K. K. Toxicity of 3,3′-methylenebis (4-hydroxycoumarin). *Proc. Soc. Exper. Biol. & Med.* **50**:228-232, 1942.
88. Jubelirer, R. A., and Glueck, H. I. Capillary fragility studies (Göthlin test) on one hundred patients receiving dicumarol. *J. Lab. & Clin. Med.* **34**:448-457, 1949.
89. Cosgriff, S. W. Effect of heparin and dicumarol anticoagulant therapy upon erythrocyte sedimentation rate. *J. Clin. Investigation* **27**:435-438, 1948.
90. Barker, N. W., Nygaard, K. K., Walters, W., and Priestly, J. T. Statistical study of postoperative venous thrombosis and pulmonary embolism. I. Incidence in various types of operations. *Proc. Staff Meet., Mayo Clin.* **15**:769-773, 1940.
91. Lillie, R. H., Buxton, R. W., and Duff, I. W. Prevention and management of thromboembolism. *Arch. Surg.* **59**:609-632, 1949.
92. Fowler, N. O. Study of certain aspects of blood coagulation in post-operative state in congestive heart failure and in thrombophlebitis. *J. Clin. Investigation* **28**:671-677, 1949.
93. Allen, E. V., Hines, E. A., Jr., Kvale, W. F., and Barker, N. W. Use of dicumarol as anticoagulant: experience in 2,307 cases. *Ann. Int. Med.* **27**:371-381, 1947.
94. Wright, I. S., Marple, C. D., and Beck, D. F. Anticoagulant therapy of coronary thrombosis with myocardial infarction. *J. A. M. A.* **138**:1074-1079, 1948.
95. LeRoy, G. V., and Nalefski, L. A. Dicumarol in experimental myocardial infarction. *J. Lab. & Clin. Med.* **33**:961-971, 1948.
96. Blumgart, H. L., Freedberg, A. S., Zoll, P. M., Lewis, H. D., and Wessler, S. Effect of dicumarol on heart in experimental acute coronary occlusion. *Am. Heart J.* **36**:13-27, 1948.
97. Kraus, A. P., Perlow, S., and Singer, K. Danger of dicumarol treatment in pregnancy. *J. A. M. A.* **139**:758-762, 1949.
98. Quick, A. J. Experimentally induced changes in prothrombin level of blood. III. Prothrombin concentration of new-born pups of mother given dicumarol before parturition. *J. Biol. Chem.* **164**:371-376, 1946.
99. Barnes, A. C., and Ervin H. K. Effect of anticoagulants on postpartum bleeding. *Surg., Gynec. & Obst.* **83**:528-530, 1946.
100. Field, J. B. Hypoprothrombinemia induced in suckling rats by feeding 3,3′-methylenebis (4-hydroxycoumarin) and acetylsalicylic acid to their mothers. *Am. J. Physiol.* **143**:238-242, 1945.
101. Parkin, T. W., and Kvale, W. F. Neutralization of anticoagulant effects of heparin with protamine (salmine). *Am. Heart J.* **37**: 333-342, 1949.
102. Cosgriff, S. W., Cross, R. J., and Habif, D. V. Excessive hypoprothrombinemia due to dicumarol. Its treatment with lyophilized plasma. *J. A. M. A.* **138**:405, 1948.
103. Duff, I. F., and Shull, W. H. Fatal hemorrhage in dicumarol poisoning with report of necropsy. *J. A. M. A.* **139**:762-766, 1949.
104. Long, M., Hurn, M., and Barker, N. W. Effect of heparin on prothrombin time. *Proc. Staff Meet., Mayo Clin.* **21**:225-229, 1946.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 36061

PRESENTATION OF CASE

A four-month-old male infant was admitted to the hospital because of cough and failure to gain weight.

The child was born by forceps delivery following a normal pregnancy. The birth weight was 7 pounds, 5 ounces, but by the seventeenth day, on discharge from the hospital where he was born, he had failed to regain his birth weight. There was no history of cyanosis. Various formulas had been tried without success, but the child frequently vomited about a half an hour following feedings. A persistent, semiproductive cough had been present since birth.

Physical examination revealed a marantic, fairly well hydrated infant weighing 7 pounds, 6 ounces. The head measured 38 cm. in diameter. There was hyperresonance over the anterior lung fields, with bronchovesicular breath sounds. Posteriorly, the left-lung field was normal to percussion and auscultation. Over the right field there was generalized dullness extending to the posterior axillary line. Bronchophony and diminished breath sounds were heard over this area. When the child was shaken, splashing succussion was heard over this area. The remainder of the examination was negative.

Examination of the blood revealed a red-cell count of 4,260,000, with 15 gm. of hemoglobin, and a white-cell count of 10,550, with 39 per cent neutrophils, 47 per cent lymphocytes, 13 per cent monocytes and 1 per cent eosinophils. The urine was essentially normal. The serum nonprotein nitrogen was 28 mg., and the protein 5.2 gm. per 100 cc., and the prothrombin time 21 seconds (normal, 16 seconds). A serum sulfonamide level

was 5.2 mg. per 100 cc. An x-ray film of the chest showed two large cysts, containing air and fluid, within the right thorax posteriorly (Fig. 1). These had displaced the right lung anteriorly, and the mediastinum to the left. The cysts were thin-walled, could not be separated from each other and possibly represented two lobules of the same cyst. The left leaf of the diaphragm appeared to be intact. Only the outer margin of the right leaf of the diaphragm was satisfactorily visualized.

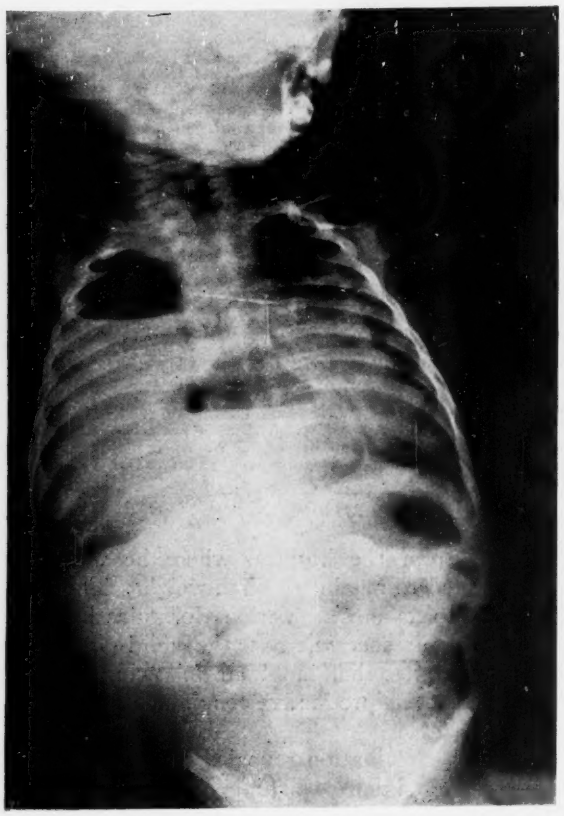

FIGURE 1.

The stomach was in the peritoneal cavity. There was no large-bowel distention, and no gas-filled large bowel was seen leading up into the chest. A week later an x-ray film showed no definite change in the amount of fluid or air in the cyst (Fig. 2).

On the tenth hospital day a thoracentesis was performed, and 90 cc. of pale-tan fluid, loaded with whitish flecks, was removed from the cyst. Some air was also withdrawn. After the fluid had been withdrawn 0.25 gm. of streptomycin was placed within the cyst cavity. Culture of the fluid showed many pleomorphic gram-negative rods identified as *Escherichia coli*.

After about three weeks' hospitalization, during which blood transfusions were given and some weight gain occurred, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD B. D. NEUHAUSER*: The signs and symptoms in this child are of significance. A persistent, semiproductive cough had been present since birth. There was no story of blood in the vomitus or description of the vomitus — whether it contained bile or anything of that sort. By the time of admission he was marantic but fairly well hydrated. The striking things in the physical examination are the hyperresonance and the splashing in the chest when the patient was shaken up a little bit.

The examination of the blood and the other laboratory findings appeared normal. When he came in there was no evidence of anemia and no

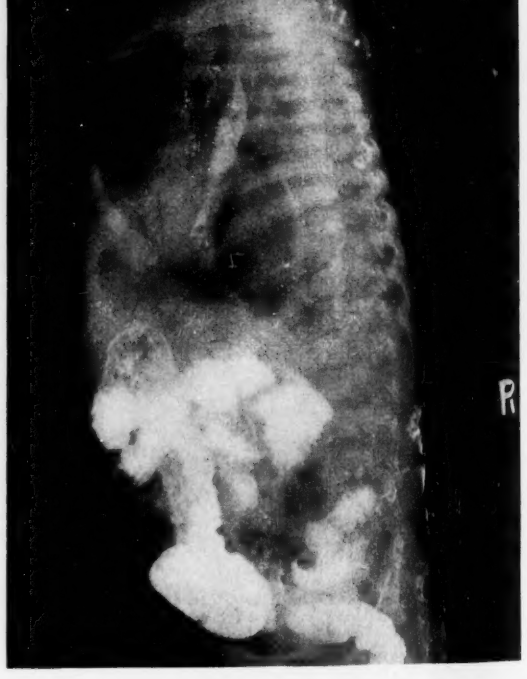

FIGURE 2.

evidence of infection as shown by blood studies, but he had one abnormal finding, a prothrombin time of 21 seconds. I do not know what significance that has in indicating liver damage. I would be inclined to dismiss it for the moment.

The next study was the x-ray examination. We have a great number of films, — twenty-four by count, — indicating that someone was puzzled. I think the most significant films were obtained on the first and second examinations taken in the other hospital. This first film (Fig. 1) is of the chest and

*Radiologist, Children's Medical Center.

the abdomen. Here we are presented with an obvious lesion, but, as so often happens, the lesion is so large and peculiar that it is very difficult to make much out of it; it is often easier when the lesion is smaller. We see some evident changes. The bones are normal, except that in the low cervical and upper dorsal spine, there is evidence of malformation. There are several double hemivertebras and widening of the interpedicular spaces — an occult spina bifida. There is no lateral film so that I cannot tell whether or not there is a soft-tissue mass such as a meningocele. There probably is not. The next striking change is the extreme shift of the heart and mediastinal shadows to the left, so that the heart lies wholly within the left thorax. The left lung appears normal. There is no evidence of inflammatory reaction, and no evidence of fluid in the left pleural space. As we go to the opposite side we can see a large, round, somewhat lobular shadow of increased density, which in the erect position appears to be a collection of fluid in a large, somewhat lobulated mass. The distribution of the mass is odd indeed, but it is because of that fact that I can hope to make the diagnosis. In the lateral film the mass appears extrapulmonary, for the lung is compressed and displaced forward so that the right lung appears to occupy the anterior lateral aspect of the right thorax and this cyst-like mass, to a great extent, is posterior. The right lung itself appears clear. There is some portion of lung herniating across the midline to the left. There is no evidence of calcium in the mass. The next x-ray examination, made a few days later, is helpful. The correct procedure was carried out. The patient was given a swallow of barium, and the examination of the gastrointestinal tract done. Here we see that the esophagus is displaced to the left along with the other shadows. Again, one can see cyst-like shadows with fluid in the right chest and, in the upright position, much more fluid. As one goes to the lateral film (Fig. 2) the esophagus is displaced forward; in other words, there are fluid-filled and air-filled cysts, apparently behind the esophagus and actually extending into the left midthorax behind the esophagus — a very unusual finding. In the gastrointestinal series, the stomach and most of the small bowel are visualized. The normal small bowel appears to lie within the peritoneal cavity. The examination of the colon was carried out in this third stage in diagnosis. The colon is normal.

Let us go back to the history. I think there are a great many questions one would like to ask. One is the nature of the white flecks. That might give the story away. An important question is, Were there a number of pus cells in the fluid? I think the percentage of pus cells might be of interest. If there were only a few, I would lean one way; if many, I would lean another. Dr. Crawford might know.

Dr. John Crawford: I do not know.

Dr. Richard H. Sweet: Dr. Lamar Soutter did the aspiration. I do not know in what laboratory the examination was done. He thought it was pus. There were white cells drained from what he thought was an infected area.

Dr. Neuhauser: At least some pus?

Dr. Sweet: That was his belief.

Dr. Neuhauser: Eventually colon bacilli were identified. In spite of the fact that on admission the patient had a normal hemoglobin and red-cell count, it is very important to know if the stool was examined for occult blood or actual hemorrhage. Was there any history of hematemesis? I would like to assume that he had a considerable amount of occult blood in the stools, since so many transfusions were given. Was he losing blood? I assume that he was.

Dr. Crawford: Several transfusions were given outside the hospital before admission. That accounts for the normal hemoglobin.

Dr. Neuhauser: Were the stools examined?

Dr. Crawford: As far as I know they were normal.

Dr. Neuhauser: We are presented with a child with symptoms dating from shortly after birth and with evidence of one clear-cut congenital malformation in the spine. The exact diagnosis of these cyst-like lesions in the chest brings up a number of conditions that might be discussed for a moment. There is nothing to suggest a collection of pleural fluid on the right. Neither the position nor the contour is that of encapsulated fluid in the pleural space. I do not believe that the patient had a cystic lesion that connected with the trachea, the bronchi or the esophagus. The lesion appears to be extrapulmonary, so that one can probably exclude an intrapulmonary cyst. It is remotely possible that he had some sort of cystic tumor. If he had, it again would have had to be communicating with the gastrointestinal tract or tracheobronchial tree. I have never seen a tumor break down and undergo extensive liquefaction with such large cysts as are evident in the roentgenograms. I thought a great deal of that possibility, but I would like to dismiss it.

Another possible lesion within the chest is a duplication of the esophagus. Certainly duplications of the esophagus may be quite large and even multiloculated with fluid. However, I have never seen one actually communicating with the esophagus, and I would not expect it to occur with any frequency whatsoever. If it did communicate I would expect more vomiting of the fluid and extensive aspiration of the fluid into the lungs. I think we can therefore exclude intrapulmonary cyst or any mediastinal mass communicating with the trachea or bronchus, and I think we can exclude duplication of the esophagus. I should rule out bronchogenic cysts and all mediastinal cysts that might be in that location.

I believe that there is only one lesion that fits this picture. It is not common, but I think there is sufficient evidence for the diagnosis and it is the only logical deduction that can be made. I believe this was one of the relatively unusual anomalies — that is, duplication of the jejunum.* These may appear much like elongated diverticula, 30 cm. or more in length, which pass through a defect in the diaphragm posteriorly and herniate into the chest. They may show only a minute opening into the jejunum so that fluid becomes trapped in the intrathoracic portion of the duplication and is not evacuated satisfactorily. A small amount of gas usually does get up into the lesion. Bleeding from the gastrointestinal tract is not uncommon, since these cysts may be lined with gastric epithelium. I have here some slides from a patient with what I believe is a similar lesion. We can see in this diagram that on the left a duplication of the jejunum arises as a straight narrow channel and passes into the hemithorax through a defect in the posterior portion of the diaphragm. This is an x-ray film of the same patient and shows a large, lobulated, soft-tissue mass in the right chest, and we can see at the extreme upper portion a small level of air and fluid. It has a different contour and somewhat different distribution, but on the whole appears to be the same lesion as that presented by the patient under discussion. The third and last slide is a similar one from still another case, but is different in distribution and more nearly conforms to the picture of the patient under discussion.

So that, in summary, I think a duplication acting as a long diverticulum arising from the jejunum and passing through the diaphragm into the right hemithorax behind the heart and behind the esophagus is the only logical diagnosis that one can make from the evidence presented. I would not be certain what this lesion was lined with. If the patient had had melena or hematemesis one would suspect the presence of gastric epithelium.

Dr. Allan M. Butler: I think Dr. Neuhauser has put his finger on what was missing in the history — namely, the poor description of the fluid obtained on tapping. It is too bad that Dr. Soutter is not here to give a better description and to include a description of the chemistry of that fluid. It would be important in arriving at the diagnosis.

Clinical Diagnosis

Bronchogenic cyst.

Dr. Neuhauser's Diagnosis

Diverticulum-like duplication of jejunum passing through defect in posterior portion of right dome of diaphragm into thorax.

*Gross, R. E., Neuhauser, E. B. D., and Longino, L. A. Thoracic diverticula which originate from intestine. *Ann. Surg.* (in press).

Anatomical Diagnosis

Duplication of intestine, esophageal and small bowel in type, arising in jejunum and passing through diaphragm into thorax.

Pathological Discussion

Dr. Sweet: I am much interested in Dr. Neuhauser's drawings because I would have said he made them from our case, especially the first one he showed. It did not look like the last one except that it had come from below the abdomen. We were unable to get as far in the diagnosis as he has gone. At operation I called it an enterogenous cyst, for want of a better name, thinking it was an esophageal duplication. It was obvious that it had no communication with the lung. It pushed the lung forward and had arisen from the mediastinum. It was quite free and cystic. As I dissected it free and had a good look at it, it appeared like the cecum with a portion of bowel leading off the bottom of it. But what surprised me was that there was an upward extension from this cyst-like bowel to the base of the neck, where it was attached to the esophagus. There was no evidence of a lumen — just a band to hold it up there. We severed that. The lower part looked like small bowel passing through the diaphragm lateral to the vena cava. It was quite apparent that by pulling it out I was merely pulling more and more of something indeterminate, and I finally decided that it was time to stop. After tying a pursestring suture around it, we allowed it to drop back from the diaphragm and took the abnormal mass out.

Dr. Tracy B. Mallory: Figure 3 shows in diagrammatic fashion the anatomical findings in this patient. There was a duplication of the intestinal tract, arising, as Dr. Neuhauser predicted, in the jejunum and passing up through the right side of the diaphragm into the thoracic cavity. The intra-abdominal portion was narrow and approximately of the same diameter as the small bowel. Above the diaphragm it widened out into a sac even longer than the stomach. At its upper pole it was attached, as Dr. Sweet has described, by a lumenless cord to the esophagus just above the aortic arch. Sections from the walls of this mediastinal structure showed two types of epithelium: one was esophageal in character with a squamous-cell lining, and the other with intestinal villi and quite typical of small bowel. We were unable to identify any gastric type of epithelium between the esophageal and small bowel portions.

A Physician: What was the postoperative result?

Dr. Mallory: The patient developed a massive collapse and uncontrollable hydrothorax and died. Death was obviously due to pulmonary atelectasis.

DR. ALFRED KRANES: Would you not expect barium to get up into the chest?

DR. NEUHAUSER: Just a swallow was given. The film may not have been taken at the right time. I wonder if the white flecks could be barium or curds of milk. We have never seen barium get up that far in the few cases that we have had.

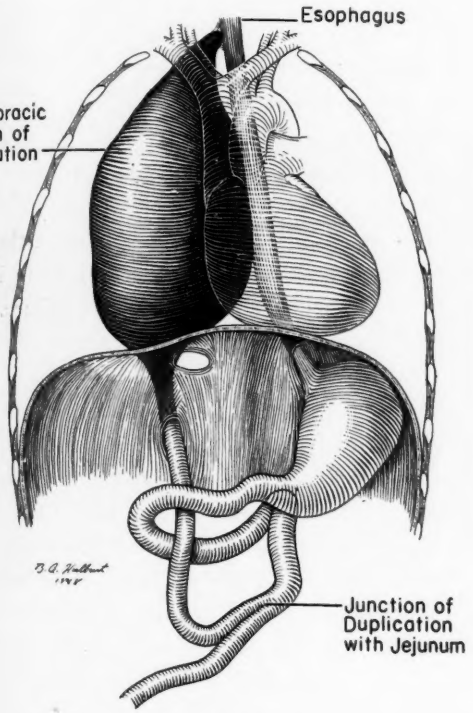

FIGURE 3.

CASE 36062

PRESENTATION OF CASE

First admission. A thirty-six-year-old stevedore entered the hospital because of increasing weakness and failing vision.

The patient was well until eight months before admission, when he noticed intermittent swelling of the ankles. Two months before admission he began to have increasing fatigue and dyspnea, edema of the face in the morning and of the ankles at night, and difficulty with vision. His doctor treated him with digitalis, but this alleviated the symptoms only temporarily. There was no history of chronic renal disease, hematuria or pyuria. There was occasional vomiting but no diarrhea.

Physical examination revealed a thin, nervous, pale, dyspneic man with engorged neck veins. The fundi showed hemorrhages and exudate, with choked disks. The teeth were carious. There were moist expiratory rales in both lung bases. The heart was enlarged, and there was a Grade I apical systolic murmur. The liver margin was down two finger-breadths. There was a tremor of the extremities, and equally increased reflexes were present throughout. The Chvostek and Trousseau signs were negative. The legs were edematous.

The temperature was 99°F., the pulse 120, and the respirations 36. The blood pressure was 190 systolic, 100 diastolic.

Examination of the blood disclosed a white-cell count of 9000, with 89 per cent neutrophils. The hemoglobin was 6 gm., and the red-cell count was 1,900,000. The serum calcium was 5.0 mg., the phosphorus 9.9 mg., and the nonprotein nitrogen 150 mg. per 100 cc. The carbon dioxide was 13, the chloride 107, and the sodium 140 milliequiv. per liter. The total protein was 5.42 gm. with an albumin-globulin ratio of 1.44. The urine showed a reaction of pH 7.0, a specific gravity of 1.012 and a ++ test for albumin, and the sediment contained many pus cells and occasional red cells and granular casts.

An x-ray film of the chest showed the heart to be enlarged in all diameters, with mottled density in both lung fields and a small amount of fluid in the pleural sinuses. An electrocardiogram was consistent with left ventricular preponderance on the basis of hypertension.

The patient was treated with rice diet, digitalis, Amphojel, calcium and vitamin D, and showed gratifying improvement. After three weeks his progress was reported as follows:

> On physical examination he remained sallow. The fundi still showed hemorrhages and blurred disk margins. The neck veins had receded. The chest was clear. The heart was enlarged as on admission, but the sounds were of good quality, with the aortic second sound greater than the pulmonic. There was no edema. Blood chemical studies showed a decline of nonprotein nitrogen to 84 mg. per 100 cc., of carbon dioxide to 31.8 milliequiv. per liter, and calcium to 8.4 mg. and phosphorus to 6.4 mg. per 100 cc. The sodium and chloride were declining, the latter to 88 milliequiv. per liter, probably as a result of the rice diet.

The patient was discharged after one month's hospitalization.

Final admission (one month later). In the interval he had been seen in the Medical Clinic and was making satisfactory progress, with a hemoglobin of 7.8 gm., nonprotein nitrogen of 90 mg. per 100 cc., and carbon dioxide of 30.6 milliequiv. per liter. The blood pressure was 170 systolic, 90 diastolic. Within the last week, however, in addition to increased dyspnea and fatigue, the patient had frequent headaches and blurring of vision, anorexia, vomiting and diarrhea (with tarry stools two or three times a day).

Physical examination revealed a semi-stuporous man with a uremic odor to the breath. There were dullness throughout both lung bases and rales throughout the chest, and an enlarged heart with

a Grade II apical systolic murmur. The reflexes were hyperactive; the Babinski reflexes were equivocal. The hands were tremulous.

The temperature was 98.6°F., the pulse 100, and the respirations 24. The blood pressure was 195 systolic, 100 diastolic.

The white-cell count was 17,500, with 82 per cent neutrophils. The hemoglobin was 6 gm. The nonprotein nitrogen was 118 mg., calcium 7.8 mg., and phosphorus 6.8 mg. per 100 cc. The carbon dioxide was 25.2, and the chloride 84 milliequiv. per liter. Examination of the urine showed a specific gravity ranging from 1.006 to 1.010, with a ++ test for albumin and occasional red cells in the sediment.

Fluids were forced by clysis, and the patient showed some mental clearing. He continued to pass tarry stools. On the tenth hospital day the temperature, pulse and respirations increased to 103°F., 120 and 28 respectively, and he developed a left anterior axillary "pleuritic" pain with a dry cough. Physical examination revealed dullness and tubular breathing in the left lower lobe and moist inspiratory rales in the left axilla. An x-ray film of the chest taken with a portable machine showed increased density in the left upper lobe, and penicillin therapy was started.

He became irrational and unresponsive and died on the thirteenth hospital day.

Differential Diagnosis

Dr. Ernest Craige*: Although this patient's symptoms were of relatively recent onset, by the time he reached the hospital, he already had severe hypertension, far-advanced cardiac and renal failure and papilledema. The earlier symptoms of swelling of the ankles, dyspnea and fatigue were largely due to congestive failure. There had been temporary relief with digitalis and, on physical examination, there was evidence of an enlarged heart, pulmonary congestion, distended neck veins and an engorged liver. The failure of the myocardium was presumably on the basis of severe hypertension. That kidney disease contributed also to the fluid accumulation was suggested by the puffiness of the face. More important evidence of renal failure was supplied by the urinary findings of low specific gravity, granular casts, red and white blood cells and albuminuria. Azotemia was very marked. Additional evidence of uremia at the time of admission was afforded by the considerable phosphorus retention and consequent reduction in serum calcium. The anemia, too, can be attributed to uremia; it was of severe degree, with the hemoglobin down to 6 gm. It appears to have been of the normocytic variety, resistant to all methods of treatment, as is usually the case in renal failure. Uremia, then, was probably responsible for the patient's pallor, tremors and hyperactive reflexes.

In the hospital, the patient was energetically treated with rice diet and measures designed to precipitate phosphorus in the intestine. These efforts were partially successful since the serum calcium rose and the phosphorus fell, although not to normal levels. There was also some improvement in the acidosis and congestive failure. On the sharply restricted salt intake, however, the chloride fell to a low level.

Following the temporary improvement, during which he was able to leave the hospital, the patient returned with symptoms of terminal uremia, including a severe colitis, and died with an intercurrent infection, probably bronchopneumonia.

The differential diagnosis here lies between essential hypertension and primary nephritis. Another possibility, pheochromocytoma, is sometimes responsible for a sustained severe hypertension. It would be extremely rare, though, for it to cause this full-blown picture of cardiorenal failure. The terminal picture in a small percentage of cases of severe essential hypertension may be marked by extreme elevation of the blood pressure, papilledema and renal failure. This syndrome of so-called malignant hypertension is often indistinguishable from that presented by a small group of patients with primary kidney disease seen for the first time in a terminal state with hypertension, uremia and papilledema. Such an end has been described in chronic pyelonephritis, polycystic disease of the kidneys and amyloid disease, as well as in glomerulonephritis. There is no evidence here of congenital cystic disease or amyloid disease so that these can be dismissed. The presence of pus cells in the urine suggests the possibility of chronic pyelonephritis, but there is no past history to suggest urinary-tract infection and no cultural evidence at present of bacilluria. Both these features, of course, may be absent late in the course of chronic pyelonephritis.

The more important possibility is glomerulonephritis. It would be helpful if there were an early

*Clinical fellow in medicine, Massachusetts General Hospital.

history to suggest an attack of nephritis or a history of albuminuria long before the present admission. No such information is available. There are, however, certain leads that help to separate this case from essential hypertension in the malignant phase. In the original description of malignant hypertension by Keith, Wagener and Kernohan,* the diastolic pressure was always considerably higher than the figure of 100 mm. of mercury as in this case. Renal failure was seldom so striking as in cases of chronic nephritis, with ability to concentrate often not severely reduced and azotemia seldom at such high levels except occasionally in the last stages. Similarly, anemia was never so severe as in chronic nephritis. These three features—the moderate hypertension and the severe degree of renal failure and anemia — are more in favor of primary kidney diseases, or specifically, glomerulonephritis, which is the diagnosis that I favor. What was the duration of the kidney disease? The history was only of eight months' duration, but it is entirely possible that the recent illness represented merely an exacerbation of a chronic process, previously undetected. On the other hand, a relentlessly progressive nephritis of less than a year's duration could be responsible for the whole picture. I know no way to determine the age of the process.

In summary, then, I believe that this patient had glomerulonephritis either chronic or subacute, with terminally a severe hypertension and cardiac failure, uremia and bronchopneumonia.

*Keith, N. M., Wagener, H. P., and Kernohan, J. W. Syndrome of malignant hypertension. *Arch. Int. Med.* **41**:141-188, 1928.

Clinical Diagnoses

Chronic glomerulonephritis.
Lobar pneumonia.
Cardiac hypertrophy.

Dr. Craige's Diagnoses

Chronic or subacute glomerulonephritis.
Bronchopneumonia.
Cardiac hypertrophy.
Uremia.

Anatomical Diagnoses

Subacute and chronic glomerulonephritis.
Lobar pneumonia.
Pericarditis, uremic.
Cardiac hypertrophy and dilatation.
Hydrothorax.

Pathological Discussion

Dr. Benjamin Castleman: Dr. Craige has correctly predicted most of the anatomical findings. The renal lesion was that of a subacute and chronic glomerular process; the kidneys had shrunk only about a third, weighing 280 gm. This means that the duration of the disease was probably not very much more than the eight months indicated by the clinical history. The precipitating cause of death was an extensive lobar pneumonia involving both lobes of the left lung. As evidence of uremia there were a fibrinous pericarditis and mucosal hemorrhages in the bowel. The heart weighed 450 gm. and showed left ventricular hypertrophy.

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THE JOURNAL does not hold itself responsible for statements made by any contributor.

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PROFESSIONAL SECLUSION

ONE of the dangers that regularly confront any nation is the acceptance of a political leadership that lacks the qualities of statesmanship.

In this country, which has had its ups and downs, its good leaders and its bad ones, its honest administrations and its corrupt ones, the form that government takes is, in the last analysis, that which a majority of the people have chosen or are willing to accept. Choice and acceptance, however, do not originate with the people but are suggested by the very leaders who have persuaded the people to follow them. In the series of crises with which this country is at present confronted, extension of the presently accepted principles of government, it is believed by many who have made a study of national economy, will in the end bring financial ruin if followed through to their conclusion.

This is the threat. In view of it the physicians of America, comprising the first large group whose freedom of action has been assailed, must assume still stronger leadership in the continuing opposition to unwarranted compulsion.

Such a call to the profession, as voiced by Dr. Herman L. Kretschmer before the Institute of Medicine of Chicago in December, when he urged physicians to "come out of their professional seclusion to take leadership as patriotic citizens in the fight to the finish against the 'welfare state,'" emphasizes the reluctance of many doctors to accept this public charge.

Professional seclusion is an apt term. The physician, equipped with the opportunity, the training and the experience for leadership, too often pursues his vocation unmindful of the occasions for broader service to which he might rise.

Like Holmes's chambered nautilus, he should leave a "low-vaulted past" and find, in greater opportunity, greater service.

1950 HEART CAMPAIGN

As a part of the national effort to control the disease that ranks first among the leading causes of death, the campaign of the Massachusetts Heart Association deserves the support of laymen and physicians alike. A goal of $6,000,000 has been set by the American Heart Association, and the organizations in Massachusetts and four other New England states will do their utmost to contribute their share.

The money raised in the campaign will be devoted to the following purposes: to finance local and national research in cardiovascular disease; to provide standards for local clinics; to support continuing programs for the advancement of professional knowledge and practice; to furnish lectures, forums and panels for discussion; to give free penicillin for the treatment of needy persons with subacute bacterial endocarditis; to plan for a co-ordinated service for children with rheumatic fever; to organize the Commonwealth into effective citizen groups; to provide information on all phases of heart disease; and to distribute free identification cards for patients with cardiac conditions, recom-

mending chemotherapeutic prophylaxis before oral surgery or tooth extraction. Among the primary projects supported by the Massachusetts Heart Association emphasis is placed on participation in the Boston Chest X-Ray Program, co-operation with the multi-phasic screening plan, a study of the best means of improving home care of ambulatory patients with heart disease, attention to rehabilitation of cardiac patients and investigation of the efficacy of treatment and methods of diagnosis of rheumatic fever.

Success in this ambitious program would greatly further progress in the recognition, treatment and follow-up care of diseases of the heart. It is to be hoped that the citizens of Massachusetts will give the campaign all possible aid and co-operation.

DIAGNOSIS OF CANCER

CANCER is obviously of extreme interest to all informed persons. This is for the general good and is resulting in earlier and better treatment, and opportunities for increased laboratory and clinical study of the disease.

Publicity also has its disadvantages. It tends to make discoveries appear to be of more immediate and practical importance than they often deserve. A distinction must be made between discoveries that are primarily interesting scientifically, and that may have practical importance only as they are developed, and those that begin with practical implications.

Thus, a reliable laboratory diagnosis for the presence of cancer would be extremely valuable from all points of view, but a test that is only 75 or 80 per cent correct has little value as a routine test, and yet has sufficient merit to warrant investigation to find out its true significance. It would certainly not be a test that any physician could use by itself alone for cancer detection, because of its inaccuracies.

As suggested by Dr. Scamman's letter published elsewhere in this issue of the *Journal*, to make such a test widespread through economic exploitation would seem even more unwise. Tests that give inaccurate evidence produce great insecurity in diagnosis rather than the security that one needs.

The work of Huggins in exploring abnormalities in the blood proteins in cancer is an important scientific investigation that deserves vigorous support. Stress should be placed on finding out why the Huggins test and analogous procedures, like the Bolen test, are positive as often as they are. This would lead to progress, whereas too early exploitation of the test as a routine may lead only to the tragedy of incorrect diagnoses and the premature discrediting of the method.

OUNCE OF PREVENTION

THE *Journal*, on July 7, 1949, commented editorially on the attitude of Dr. James F. Brailsford, director of the x-ray and radium departments at Birmingham Hospital, England, in opposing mass x-ray checkups or, indeed, any kind of checkup of those who have no symptoms of disease. Dr. Brailsford's utterances were immediately seized upon by the organized opponents of orthodox medical practice as representing something little less than gospel truth. Dr. Brailsford had at that time been a recent visitor to this country.

The esteem in which Dr. Brailsford is held in his native land is brought out in the following letter published in the *British Medical Journal* for October 22, 1949:

> *Sir*, — His colleagues in Great Britain know enough about Dr. James F. Brailsford to discount the various extravaganzas in which he indulged in his article entitled "Modern Trends in Radiology" (October 1, p. 724). Dr. Peter Kerley (October 15, p. 870) has drawn attention to some of the grosser mis-statements, and I would merely like to draw attention to the absurdity of his recommendation that medical students should perform upon one another "every kind of injection, including ventriculography, myelography, arteriography, etc." This from the director of radiological studies in living anatomy of a distinguished university.
>
> It is disquieting, however, to learn from a footnote that Dr. Brailsford has been talking such nonsense in various parts of the United States. It is important that our American colleagues should realize that these views are Dr. Brailsford's own and do not represent the consensus of intelligent radiological opinion in this country, and it is with that object that I write this letter. — I am, etc.,
>
> S. COCHRANE SHANKS
>
> London, W. I.

Dr. Shanks may rest assured. No medical men in this country accepted Dr. Brailsford's views as representing British medical opinion, nor were they

taken seriously by any persons other than those whose interests they served to support.

As Boston's mass chest x-ray program came to a successful close, attention was more sharply focused on the pilot health protection clinic now in operation at the New England Center Hospital. This unique adventure in preventive medicine, operating according to the principles that Dr. Brailsford decries, has achieved national prominence. Already appointments have been made for months ahead, by appreciative persons from all over New England.

The beneficial results of industry, simple food, and regular habits, are seen in the fact that the Society of United Brethren (Shakers) at Enfield, Conn., numbers two hundred and sixty-eight, and not a death has occurred among them for fourteen months.

Boston M. & S. J., *February 6, 1850*

OBITUARY

RAYMOND STANTON TITUS
1883–1949

Dr. Raymond Stanton Titus died on Christmas Day, 1949, at the age of sixty-six. He is survived by his wife, three children and seven grandchildren.

After graduation from Harvard College in 1905 and the Harvard Medical School in 1909 he served an internship in surgery at the Boston City Hospital and then embarked on his career as a specialist in the field of obstetrics.

He belonged to the Massachusetts Medical Society and the New England Obstetrical and Gynecological Society and was a fellow of the American College of Surgeons and the American Medical Association; he was one of the early certificants of the American Board of Obstetrics and Gynecology. At one time or another he was a member of the staffs of the Boston Lying-in Hospital, the Long Island Hospital and the Florence Crittenton Home. Before his retirement because of age, he was obstetrician-in-chief at the Faulkner Hospital and one of three obstetricians to the Massachusetts General Hospital; up to the time of his death he continued on the consulting staffs of these two institutions.

During his early days he tried his hand at teaching, serving from 1915 to 1921 as assistant in obstetrics at Harvard Medical School. He wrote occasional clinical articles, regarding as his most significant efforts in medical literature his papers on hemorrhage during pregnancy and on puerperal sepsis.

In the Massachusetts Medical Society he acted for several years as chairman and, later, as secretary of the Section of Obstetrics and Gynecology; in this capacity he helped to edit a series of short articles dealing with obstetric problems and maternal welfare that appeared each week in the *New England Journal of Medicine*.

This gives a short review of his medical career. Essentially, however, he was a practitioner of medicine. Once he wrote of himself that his chief aversions were snobbishness and dishonesty, and that it was his philosophy to get all the pleasure from life that he could, besides striving to be honest and charitable to everyone. He was so competent, unselfish and conscientious that he quickly attained a high degree of professional success; by his skill, his wisdom and his integrity, and by the way he taught his own simple concepts of the art of living, he helped countless mothers to bring children into the world happily and safely.

He was a worthy pupil of the Boston School of Obstetrics — of Walter Channing, William Lambert Richardson and Franklin Spilman Newell. Like them, he exemplified the best type of New England doctor.

R. F.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

McMAHON — William E. R. McMahon, M.D., of Boston, died on November 19. He was in his sixty-second year.

Dr. McMahon received his degree from Harvard Medical School in 1916.

Two sisters survive.

STONE — Ella G. Stone, M.D., of Boston, died on January 20. She was in her eighty-fifth year.

Dr. Stone received her degree from Tufts College Medical School in 1894. She was formerly ward physician in Lawrence and a member of the staffs of Boston Psychopathic Hospital and Boston Dispensary.

A son survives.

CORRESPONDENCE

CANCER TEST

To the Editor: Within a week or ten days, several physicians have written or telephoned to me and to Dr. Ernest M. Daland, chairman of the Professional Committee of the Massachusetts Division of the American Cancer Society, to inquire about the usefulness of the iodoacetate index test (Huggins test) for the diagnosis of cancer.

These inquiries have been stimulated by an advertisement of the American Reagents Company, 3640 N. Broad Street, Philadelphia 40, Pennsylvania, which indicates that special

reagents, furnished by this company, make possible "a simple, cheap and reasonably sure blood test for cancer." The advertisement of this company indicates that a positive blood test shows the presence of cancer, and a complete set of reagents to perform the test costs $10.00.

An evaluation of the iodoacetate test just now completed, with the aid of a grant from the Massachusetts Division, Inc., of the American Cancer Society, shows that although the test is of great potential interest, it has not lived up to its initial promise. This evaluation, done under the immediate supervision of Dr. Shields Warren, pathologist, New England Deaconess Hospital, Boston, shows that the iodoacetate test (Huggins test) does not constitute a useful tool for the diagnosis of the presence of cancer.

In view of the interest of physicians in this test, I shall appreciate your publishing this letter in an early issue of the *Journal*.

CLARENCE L. SCAMMAN, M.D.
Medical Director

American Cancer Society
(Massachusetts Division), Inc.
Boston

REGARDING "COLD CURES"

To the Editor: An an allergist, I read the editorial "Antihistaminic Cold Cures and Modern Sales Methods" in the January 19 issue of the *Journal* with a great deal of interest and appreciation. You have presented the facts briefly yet clearly.

I know you would be doing both the patients and the medical profession a real service if you could reprint this editorial on a single face page, which could be distributed to all interested physicians for use in their waiting rooms. I know that only by this method will the medical profession be able to combat in part the unfair practices promulgated by the commercial houses and foisted on the public.

HARRY HERSHEY, M.D.

Jersey City, New Jersey

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Studies from the Rockefeller Institute for Medical Research. Reprints. Vol. 138. 8°, paper, 589 pp. New York: Rockefeller Institute for Medical Research, 1949.

Introduction to Functional Semantics. By Joseph G. Brin, LL.M., Litt.D., professor of semantics, Boston University School of Public Relations. With a foreword by Maxwell H. Goldberg, Ph.D., professor of English, University of Massachusetts. Assisted by Lloyd S. FitzPatrick, A.B., Ed.M. 12°, paper, 202 pp. Boston: National Press Corporation, 1949. $3.00.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the new Cheever Amphitheater, Dowling Building, Boston City Hospital, on Tuesday, February 14, at 8 p.m.

PROGRAM

Observations Relating to Ascites and Edema in Patients with Liver Disease. George J. Gabuzda, Jr., Henry S. Treager and Charles S. Davidson.

Distribution and Fate of Antigen in the Animal Body. Edward H. Kass, William H. Macmillan, Mary I. Kenrick and F. H. L. Taylor.

Observations on Epileptic Myoclonus. Wesley Watson and D. E. Denny-Brown.

ALPHA OMEGA ALPHA

Under the auspices of the Tufts chapter of Alpha Omega Alpha, Dr. Stanley E. Bradley, assistant professor of medicine, Columbia University College of Physicians and Surgeons, will lecture on "Renal Mechanisms of Adaptation" in the auditorium of the Beth Israel Hospital, Boston, on Tuesday, February 14, at 8 p.m. The lecture is open to the medical profession.

GREATER BOSTON MEDICAL TECHNOLOGISTS ASSOCIATION

A meeting of the Greater Boston Medical Technologists Association will be held in the amphitheater of the Evans Memorial, Massachusetts Memorial Hospitals, 65 East Newton Street, Boston, on February 14, at 7:30 p.m. Dr. David Skinner will speak on the subject "Differentiation of Pathogenic Bacteria."

NEW ENGLAND CONFERENCES ON ALLERGY AND RELATED SUBJECTS

The New England Conferences on Allergy and Related Subjects will be held on Wednesday afternoon and evening, February 15. The afternoon program, consisting of the presentation of cases of bronchial asthma and illustrating the use of special technics in diagnosis and the use of Cortisone in treatment, will be held in the amphitheater of the Evans Memorial Hospital, 65 East Newton Street, Boston, from 3:30 p.m. to 5.30 p.m.

At the evening program, which will take place in the State Suite of the Copley Plaza Hotel, Boston, at 8:30 p.m., Dr. Bram Rose, of McGill University Faculty of Medicine and the Royal Victoria Hospital, Montreal, will discuss "The Effect of ACTH on Bronchial Asthma and Other Conditions of Hypersensitivity."

A dinner at the Copley Plaza Hotel, Boston, for the convenience of those attending the program, will take place at 7:00 p.m. Reservations may be made on or before February 10 by application to Dr. Irving W. Schiller, 65 East Newton Street, Boston 18, Massachusetts, enclosing a check for $4.50 to cover the expenses of the dinner.

All members of the medical profession are cordially invited to both the afternoon and evening meetings.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A meeting of the New England Society of Physical Medicine will be held in the lecture hall of the Nurses' Home, New England Baptist Hospital, 220 Fisher Avenue, Roxbury, Massachusetts, on Wednesday, February 15, at 8 p.m. Drs. Hollis L. Albright and Richard C. Kerr will speak on the subject "Implementary Management of Peripheral Vascular Disease."

A symposium and discussion period will follow.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital, on Thursday, February 16, at 8:15 p.m.

A symposium entitled "Recent Advances in the Diagnosis and Treatment of Bronchial Asthma" will be presented. Dr. Francis C. Lowell will discuss the problem in adults. Dr. Lewis Webb Hill will consider the subject in children. There will be a discussion by Drs. Nathan Gorin, Hyman L. Naterman and Irving W. Schiller.

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, February 21, at 12 noon.

A sound and color film will be shown on the subject "Role of Gastroscopy in the Diagnosis and Treatment of Gastric Pathology." Dr. I. R. Jankelson will discuss the subject "Peptic Ulcer."

Physicians are cordially invited to attend.

MASSACHUSETTS TRUDEAU SOCIETY

The winter meeting of the Massachusetts Trudeau Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Thursday, February 23, at 8:15 p.m. The sub-

ject of the meeting will be "Extrapulmonary Tuberculosis," and the program is as follows:

Genitourinary Tuberculosis. Dr. Fletcher H. Colby.

Treatment Problems in Hematogenous Tuberculosis. Dr. Carl Muschenheim, associate professor of clinical medicine, Cornell University Medical College.

Physicians and medical students are cordially invited.

AMERICAN GOITER ASSOCIATION

The annual meeting of the American Goiter Association will be held in the Shamrock Hotel, Houston, Texas, on March 9, 10 and 11.

The program will consist of papers dealing with goiter and other diseases of the thyroid gland, dry clinics and demonstrations.

Further information regarding the meeting may be obtained by application to George C. Shivers, M.D., corresponding secretary, American Goiter Association, Colorado Springs, Colorado.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A regular meeting of the New England Society of Anesthesiologists will be held in the auditorium of Building A, Boston University School of Medicine, Boston, on Tuesday, March 14, at 7:30 p.m. Dr. Donald E. Brown will speak on the subject "Fluid Therapy in Surgical Patients."

CORNELL ALUMNI DAY

Cornell University Medical College will hold its annual Alumni Day on March 23. The second annual award to an alumnus for outstanding contributions to medicine will be conferred upon Dr. David P. Barr, professor of medicine at Cornell, at the end of a scientific program presented by well known alumni of the College. The speakers will be Dr. Armand J. Quick, of Milwaukee, whose subject is "A New Concept of Venous Thrombosis,"; Dr. Paul F. Russell, of New York City, whose subject is "International Preventive Medicine"; and Dr. Harry M. Rose, of New York City, whose subject is "Studies on the Inhibition of Influenza Virus by Secretions of the Human Respiratory Tract."

The scientific program will also include operating clinics and the presentation of papers by the staff of the Second (Cornell) Divisions at Bellevue Hospital, and an exhibit covering research work at the New York Hospital–Cornell Medical Center.

SUFFOLK DISTRICT CENSORS' MEETING

The censors of Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, Boston, on Thursday, May 4, at 4 p.m.

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

The sixty-first annual meeting of the American Association of Genito-Urinary Surgeons will be held at the Hotel Hershey, Hershey, Pennsylvania, on May 24, 25 and 26.

Titles of papers should be sent to the Secretary as soon as possible. Contributions to the program will be accepted up to February 25, unless the program is filled before that time.

AMERICAN CANCER SOCIETY CLINICAL FELLOWSHIPS

A limited number of fellowships given by the American Cancer Society offer graduates in medicine opportunities for postgraduate training, emphasizing diagnosis and treatment of cancer. Fellowships available on and after July 1, 1950, will be awarded for one year and are renewable to and including three years. Fellowships are awarded to *institutions only* upon application by deans, executive officers or department heads. Persons desiring such fellowships should consult the appropriate authority in the institution of their choice.

Applications for Fellowships for the year 1950-51 must be submitted prior to February 15, 1950. Further information may be obtained from the Professional Education Section of the American Cancer Society, 47 Beaver Street, New York 4, New York.

ROYAL SOCIETY OF EDINBURGH

A David Anderson-Berry Silver-Gilt Medal, together with a sum of money amounting to about £100, will be awarded during 1950 by the Royal Society of Edinburgh to the person who, in the opinion of the Council, has recently produced the best work on the therapeutic effect of x-rays on human diseases.

Applications for this prize are invited. They may be based on both published and unpublished work and should be accompanied by copies of the relevant papers.

Applications must be in the hands of the General Secretary, Royal Society of Edinburgh, 22 George Street, Edinburgh 2, not later than March 31, 1950.

LABORATORY COURSES AT COMMUNICABLE DISEASE CENTER, ATLANTA, GEORGIA

The schedule of laboratory courses given by the Communicable Disease Center for 1950 has been revised to include an additional one-week course in laboratory diagnosis of enteric diseases, introductory enteric bacteriology, to be given March 20-24; an additional two-week course in laboratory diagnosis of tuberculosis, to be given December 4-15; change in the dates of the previously announced three-week course in the laboratory diagnosis of tuberculosis to August 21–September 7, instead of the dates previously announced; and an additional one-week course in serologic diagnosis of rickettsial diseases, to be given November 6-10.

REGULAR CORPS EXAMINATION FOR MEDICAL OFFICERS IN UNITED STATES PUBLIC HEALTH SERVICE

A competitive examination for appointment of medical officers in the Regular Corps of the United States Public Health Service will be held on May 15, 16 and 17, 1950. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to the homes of candidates.

Appointments will be made in the grades of assistant surgeon (equivalent to Army rank of first lieutenant) and senior assistant surgeon (equivalent to captain). All commissioned officers are appointed to the general service and are subject to change of station and assignment as necessitated by the needs of the Service, although consideration is given to the officer's preference, ability, and experience. Appointments are permanent and provide opportunities to qualified physicians for a life career in clinical medicine, research and public health.

An applicant for appointment in the grade of assistant surgeon must be a United States citizen at least twenty-one years of age with a degree from a recognized medical school and at least seven years of educational training and professional experience subsequent to high school. The requirements for appointment in the grade of senior assistant surgeon are the same except that the educational training and professional experience subsequent to high school must total at least ten years.

Applicants who will complete these requirements within nine months of the date of the written examination will be admitted, but may not be appointed until they meet the above requirements. Physicians who are successful in the examination and are now serving internships will not be placed on active duty in the Regular Corps until completion of internship. The examination will include an oral interview, physical examination, and written objective tests covering basic medical sciences, including anatomy, physiology, biochemistry, microbiology and pathology; practice of medicine, comprising internal medicine (including neurology and psychiatry), therapeutics and toxicology, pediatrics, and medical problems of obstetrics and gynecology; practice of surgery, including surgery, orthopedics, gynecology and obstetric procedures; and preventive medicine and public health.

Application forms and additional information may be obtained from the Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C. (Attention: Division of Commissioned Officers). Applications received after April 17, 1950, cannot be accepted.

(Notices concluded on page xiii)

NOTICES (*Concluded from page 234*)

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

FEBRUARY 13. Delta Omega Lecture. Page 196, issue of February 2.

FEBRUARY 14. Alpha Omega Alpha. Page 233.

FEBRUARY 14. Greater Boston Medical Technologists Association. Page 233.

FEBRUARY 14. New England Society of Anesthesiologists. Page 76, issue of January 12.

FEBRUARY 14. Harvard Medical Society. Page 233.

FEBRUARY 15. New England Conferences on Allergy and Related Subjects. Page 233.

FEBRUARY 15. New England Society of Physical Medicine. Page 233.

FEBRUARY 16. Greater Boston Medical Society. Page 233.

FEBRUARY 18. Springfield Hospital. Page 196, issue of February 2.

FEBRUARY 20. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

FEBRUARY 20. Hartford Medical Society. Page 160, issue of January 26.

FEBRUARY 20-23. American Academy of General Practice. Page 252, issue of August 11.

FEBRUARY 21. South End Medical Club. Page 233.

FEBRUARY 21. Springfield Hospital. Page 196, issue of February 2.

FEBRUARY 23. Massachusetts Trudeau Society. Page 233.

MARCH 6. New England Cardiovascular Society. Page 724, issue of November 3.

MARCH 9. Neck Tumors — Problems of Diagnosis and Management. Dr. Joseph Tartakoff. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

MARCH 9–11. American Goiter Association. Page 234.

MARCH 14. New England Society of Anesthesiologists. Page 234.

MARCH 23. Cornell Alumni Day. Page 234.

APRIL 17. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

APRIL 24–28. National Tuberculosis Association. Page 678, issue of October 27.

APRIL 26. New England Obstetrical and Gynecological Society. Rhode Island Hospital and Providence Lying-in Hospital, Providence, Rhode Island.

MAY 3. Norfolk District Medical Society Anniversary Dinner.

MAY 4. Suffolk District Censors' Meeting. Page 234.

MAY 14–19. International and Fourth American Congress of Obstetrics and Gynecology. Page 160, issue of January 26.

MAY 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 24–26. American Association of Genito-Urinary Surgeons. Page 234.

JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

DISTRICT MEDICAL SOCIETIES

NORFOLK

FEBRUARY 28.

MARCH 28.

MAY 3. Anniversary Dinner.

SUFFOLK

MAY 4. Censors' Meeting.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 16

THURSDAY, FEBRUARY 16

8:15 p.m. Greater Boston Medical Society. Auditorium, Beth Israel Hospital.

FRIDAY, FEBRUARY 17

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

MONDAY, FEBRUARY 20

*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, FEBRUARY 21

*12:00 m. South End Medical Club. Headquarters, Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*Open to the medical profession.

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